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THE INFLUENCE OF EMOTION IN PRECIPITATING CONVULSIONS.*

(Preliminary Report.)

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A 13-year-old boy who gave the history and showed the neurological signs of a cerebral injury at birth subsequently developed typical grand mal seizures. As a child he had been badly bitten by a dog. All the convulsions but one occurred on seeing a dog.

In this case it is evident that there are two etiological factors: first the birth injury with subsequent cerebral scar. This factor is stationary, continuously present and may be considered as the predisposing factor. The second factor is the fear produced by the sight of a dog. This factor, present only immediately preceding the attacks, may be called the precipitating factor. The common predisposing factors are: abnormalities of the central nervous system, such as congenital malformation, trauma, inflammation and neoplasm. A well-recognized precipitating factor, particularly in early childhood, is the onset of any acute infection. That emotion may be an important precipitating factor is the thesis of this report.

A study of the literature shows that emotion is often mentioned as one of the immediate causes of convulsions. Very few statistics are available, however. Gowers,[1] 1901, in a study of 1665 epileptic patients, found over 230 cases in which " fright " was given as the inciting cause for the first seizure. Rows and Bond [2] describe many cases where terror in war was responsible.

During the past three and a half years an investigation has been made to determine how frequently emotion acts as a precipitating factor. Forty-two unselected private patients have been studied. The ages varied from 10 to 53 years. All suffered from generalized convulsions with loss of consciousness.

*Read at the eighty-ninth annual meeting of The American Psychiatric Association, Boston, Mass., May 29–June 2, 1933.

In 31 of these 42 patients a direct relationship has been found between emotion and one or more of the major convulsions. In several instances all or nearly all the attacks have been immediately preceded by strong emotion, usually fear, guilt or frustration. That such emotion had causal relation to the convulsions is indicated by the fact that in eight patients major or minor attacks have been precipitated under observation by a discussion of the emotional difficulty. In three patients attacks apparently could be precipitated by the physician at will by such discussion.

In some cases the relation of the disturbing emotion to the attack is obvious, and clearly evident to the patient, as in the case of a 17-year-old girl, subject to petit mal attacks for several years, whose first grand mal seizure occurred within two hours of being forced by her family to break off her engagement to a man of whom they disapproved. More often the patient is unaware of the relationship of emotion to the attacks, particularly when there is a strong tendency for the patient to suppress the disturbing emotion from consciousness. Psychotherapy has been of definite value in several of these patients, not only by helping them to a better adjustment of their major conflicts, but more specifically by bringing back to consciousness the suppressed emotion so that the patient may see clearly the relationship of the emotion to the attack. In several instances such insight has been followed by a marked reduction in the number of attacks, as well as a decided change in the patient's outlook on life.

It should be emphasized that many of these patients, in whom emotion acted as a precipitating factor, had definite evidence of organic brain disease (predisposing factor). One had a cerebral neoplasm; others showed definite evidence in the history or at examination, of birth injury or cerebral trauma. These cases will be reported in detail at a later date.

The physiological mechanism by which emotion can precipitate a convulsion in a predisposed individual is of particular interest and deserves study. The theory that stimulation of the sympathetic nervous system by emotion plays an important rôle is supported by the fact that convulsions are occasionally precipitated by pain and by cold. Emotion, pain and cold are well-known stimulators of the sympathetic nervous system. Moreover, the onset of acute infections frequently precipitates convulsions in predisposed indi-

viduals. Here again the sympathetic nervous system is strongly stimulated. Whether the stimulation of the sympathetic nervous system precipitates the convulsion by cerebral vasoconstriction or by some other mechanism is not known.

CONCLUSIONS.

1. In 31 of 42 private patients suffering from generalized convulsions, emotion was a precipitating factor.

2. In eight patients major or minor seizures were precipitated by emotion under observation.

3. Evidence is brought forward to show that the emotion acts through stimulation of the sympathetic nervous system.

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DISCUSSION.

DR. STANLEY COBB (Boston, Mass.).—I am especially interested in this work because only in the last four years have we had our eyes opened to this aspect of epilepsy. As Dr. Fremont-Smith says we have had a rather startling experience.

I would like to add a word about treatment. If I may use the blackboard here, I can express my ideas perhaps a little more easily (see Fig. 1). At the end of an examination of an epileptic, after we have had him in the hospital for a week's observation (which is almost minimum), I often have to interview the parents to analyze and explain the whole situation. For this I use a chart modified from that designed by Adolf Meyer and described by me in Med. Clinics of North America, 3: 1137, 1920. I indicate by arrows the burdens of abnormality that these individuals have to bear; a long heavy arrow means a heavy load over a long while; all the arrows added together make a burden on the nervous system that causes symptoms. The abnormalities may be in the environment or in the organism.

One of my recent patients exemplifies this especially well: A young woman of 21 at the age of 9 had cranial trauma and two months later onset of convulsions. She has seen many doctors and had many treatments. A régime of high enemas at 12 did no good; a nine months trial of dehydration at 18 made her worse; "lutein" has helped her irregular menses, but has not affected her fits; luminal helped but has been used excessively. Because the attacks began in the left leg and slight but distinct neurological abnormalities were noted on the left side, Dr. Wilder Penfield operated upon her at the

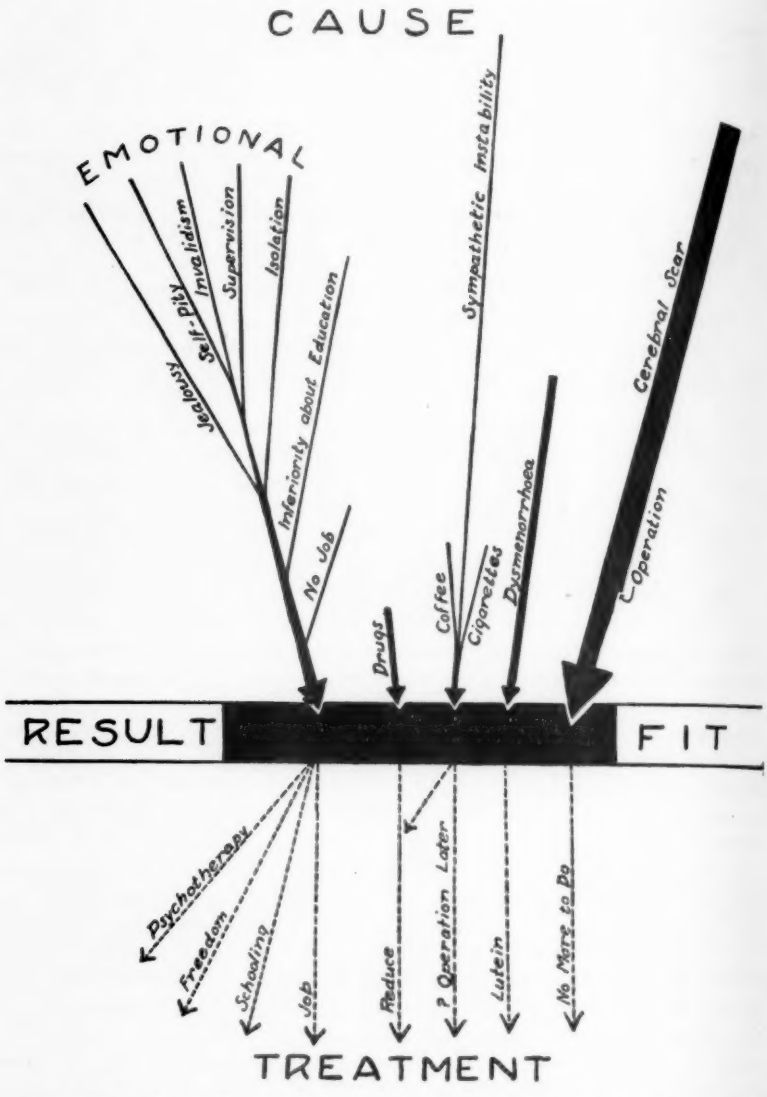

FIG. 1.—In this patient various causes (arrows above the black rectangle indicating bad mental and physical hygiene, pathology, etc.) impinge on her all at once, and by overloading an already damaged nervous system precipitate a convulsion (indicated by the black rectangle). The factors vary from time to time and this constellation of events only indicates the genesis of one fit. Below are divergent arrows showing how the nervous loads may be dissipated and better borne (*i. e.*, treatment).

age of 19 and found adhesions over the right frontal lobe, excessive vascularity of the cortex and unstable arteries. These were actually observed in vascular spasm with concomitant anemia of the lower part of the motor cortex and convulsion especially in the left face. (See Case II, Fig. 2, Penfield, W.: Annals Int. Med. 1933, 7: 306.) Removal of the "trigger point" in the cortex where a weak faradic current precipitated a convulsion (right superior frontal convolution, see Penfield's Fig. 2) caused temporary hemiparesis, but eventual diminution in number and severity of the attacks. Eighteen months later she went through a severe emotional experience, thereafter there were more "minor seizures," but many of these were probably anxiety states as no clouding of consciousness took place. The emotional element was great. Since the age of 10 she had been supervised meticulously, her varied and prolonged treatments had given her the "invalid habit," she was full of self-pity, said she was "utterly lonely" and could not mix with other girls or boys of her own age. She had had no regular schooling and could get no job.

To evaluate all the factors mentioned in this complex picture is difficult, but important, if one is to help this girl who is not only epileptic but hypochondriacal, psychoneurotic and drugged with luminal, coffee and cigarettes. Charting the factors (Fig. 1) helps a great deal to make the problem concrete.

Since the age of 9 there has been a *cerebral cortical scar;* this is the principal cause of the fits; it has been treated surgically in the most scientific manner, nothing more can be done.

The arteries of the brain were observed in spasm; there are other indications of *vasomotor instability,* but the poor general hygiene of the patient may be responsible for this especially the excessive coffee and cigarettes. An operation to denervate the cerebral arteries by sympathectomy was considered, but it was deemed unwise to operate again upon her. General hygiene, physical training, reducing coffee and cigarettes all may help the vasomotor instability (which is probably constitutional). The operation is indefinitely postponed, but may be used later as an emergency reserve measure if other measures fail.

Luminal has been used for several years; for the last two years 3 grs. per day have been given. She has been rather depressed and dopey from this and her eyes often looked sleepy. This medicine is to be discontinued for a period of observation, during which general hygiene, both mental and physical, is to be emphasized. *Lutein* has been found to help her painful and irregular menses; this is to be continued.

The *emotional factors* are numerous. Taken singly they do not seem important; added together, however, they make a burden of anxiety, unhappiness and self-pity that is devastating; the patient is having no satisfaction out of life. It is here that we feel we can do the most hopeful therapy. She needs schooling and training to give her self-confidence; she must get away from home and be under less fearful and more objective supervision; there will then be more feeling of freedom. A job has been arranged for her part time. Psychotherapy to give her insight into what is being done has been arranged for several hours a week.

When such a "new deal" can be arranged for a patient, there is reason for optimism regarding the prognosis even in cases of "traumatic epilepsy." The fact that one has a scar in one's brain does not make convulsions a certain result. It is a case of summation of nervous load. When many of the factors indicated by the arrows in Fig. 1 impinge on the patient's nervous system at once a seizure results. It is a case of the "camel's back" and many "straws." One cannot take away the scar which is the original and biggest part of the nervous load, but if the other straws are removed, the patient may well go on for years without a seizure. Symptomatically she may be "cured." And that is all the patient cares about.

That all the factors contributing to the "nervous load" are not equally important from an etiological standpoint is indicated by the varied length and size of the arrows in Fig. 1. Certain especially conditioned reactions, however, may have a most dramatic effect; for example, the fits precipitated in the 13-year-old boy with cerebral birth injury, by fear of dogs. When such a specific relation of a fit to an emotional situation can be demonstrated, the phenomenon is almost a "conditioned reflex." It is in these cases that psychotherapy can be most immediately helpful.

Dr. S. Bernard Wortis (New York City).—I would like to ask Dr. Fremont-Smith whether in any of these reported cases he has had experience with the use of ergotamine tartrate, or any other drugs acting on the sympathetic nervous system.

Dr. George Van Ness Dearborn (New York City).—I would like to ask Dr. Fremont-Smith if the emotion has more influence in bringing on an attack which might be on the borderline between the hysterical attack and truly epileptic attack than it could on the really epileptic. My point of view is that there is a continuum in a great many cases. I should be glad to have Dr. Fremont-Smith's opinion on that matter, if it isn't an especially hysterical seizure which very frequently simulates the epileptic seizure which is brought on by the minor emotions.

Dr. Frank Fremont-Smith (Boston, Mass.).—In answer to Dr. Dearborn's question, I think it is often difficult, as he says, to distinguish between so-called hysterical reactions and so-called epileptic reactions.

However, many of our patients showed clear evidence of having organic disease of the brain and there was no question about their having major generalized convulsions with loss of consciousness, biting of the tongue, injury, often incontinence. If this describes epilepsy, these patients had epilepsy. "Epilepsy" is not a disease, but a symptom complex. In these patients the major convulsive seizures were frequently precipitated by emotion.

I have made no observations concerning ergotamine tartrate.

When an incident has been forgotten, an appropriate stimulus will bring it back to memory. If the incident was accompanied by a disagreeable

emotion, the memory of it may be strongly suppressed. Under such circumstances the stimulus may fail to bring the incident back to consciousness. It may, however, re-awaken the emotion originally associated with it, together with the vegetative responses appropriate to the emotion. Under these circumstances, as Cannon (Bodily Changes in Pain, Hunger, Fear and Rage, by Walter B. Cannon, 2d edition, page 252. D. Appleton & Company, New York, 1929) has indicated, the vegetative responses to the emotion may become exaggerated and lead to symptoms. The particular symptom produced depends upon individual susceptibility or predisposition. One patient will have an attack of angina pectoris. Another will faint. A patient predisposed to seizures will have a convulsion.

The aim of psychotherapy in such patients is twofold: First to help the patient to make a better adjustment in general, and second to discover and bring back into consciousness the memory or memories which have been suppressed. When this has been accomplished, stimuli previously adequate no longer evoke exaggerated vegetative responses and no longer lead to convulsions.

RESPIRATORY METABOLISM OF EXCISED BRAIN TISSUE.*

I. The Respiratory Quotient; Carbohydrate and Lactic Acid Utilization.

By S. BERNARD WORTIS, M. D., New York City.

The fundamental work of Otto Warburg on tumor tissue respiration has directed the attention of some to the study of the metabolism of nervous tissue.

Experimental work on oxidations in the central nervous system are not new. Hill and Nabarro in 1895 endeavored to measure the oxygen consumption of animals' brains before and after convulsions induced by absinthe while the animals were under chloralose anesthesia. Herter (1905) showed that methylene blue injected into the blood of animals was rapidly reduced by the brain, indicating a considerable brain oxygen utilization. Alexander (1912), Schmidt (1927), Winterstein (1917), Tashiro (1922), Gerard and Meyerhof (1927), Warburg (1924), Loebel (1925), Fenn (1927) and Holmes and Holmes (1926) have all contributed variously to our knowledge of the oxidative metabolism of central and peripheral nervous tissue.

Downing, Gerard and Hill (1926) demonstrated an increased oxygen consumption by frog nerve on stimulation. Tashiro (1908), Parker (1925) and Fenn (1927) have proved an increase in the CO_2 production on stimulating peripheral nerve. Winterstein (1920) measured and proved the disappearance of sugar from a solution in which nerve was immersed and also demonstrated a greater disappearance of the sugar from the medium when the nerve was stimulated. E. G. Holmes, Gerard and Solomon have shown that frog nerve stimulated in various ways and for periods up to nine hours have the same content of free sugar, glycogen and lactic acid as their resting controls. They concluded that the extra energy required for nerve activity is not the result of the oxidation of any of these substances from the nerve content itself.

*From The Laboratory of Experimental Neurology—Department of Laboratories—Bellevue Hospital, New York City. Read at the eighty-ninth annual meeting of The American Psychiatric Association, Section on Convulsive Disorders, Boston, Mass., May 29–June 2, 1933.

Studies of central nervous tissue metabolism are more difficult and two methods have to date yielded valuable information:

1. The technique elaborated by Barcroft and Kato (1915) and modified by Warburg (1923) and Dickens and Simer (1931) in which the respiratory quotient of small bits of living tissue can be determined by an accurately calibrated vessel-manometric unit—in which pressure change is converted into volume change by means of a simple proportionality factor, varying with the gas measured (oxygen or carbon dioxide) and the volume of the vessel in which the determination is made.

2. The second method used to study the metabolism of brain tissue is that of determining the respiratory quotient of the organ by measuring and analyzing simultaneous samples of blood, entering and leaving the brain, for CO_2 and O_2. By this method the respiratory quotient is simply the percentage increase of CO_2 divided by the percentage decrease of O_2. Himwich and his collaborators have given us most information for brain tissue by this technique. Lennox (1930) using the technique (to obtain internal jugular vein and internal carotid artery blood) described by Myerson, Halloran and Hirsch (1927) studied the oxygen and CO_2 content of blood from the internal jugular and other veins—and showed that "both the respiratory quotient and the sugar consumption of the human brain are a trifle higher than those of the superficial tissues of the arm."

The rôle of carbohydrates, lactic acid and succinic acid in brain metabolism have been studied by Holmes and Quastel and Wheatley.

Procedure.

At the Bellevue Hospital Laboratory of Experimental Neurology we have applied the technique described by Warburg to the study of some oxidations in brain tissue. For most of this work adult rat brain was used. We have made wet weight determinations on minced brain rapidly removed, after sudden decerebration without anesthesia. The Ringer solution is made up according to the formula given by Warburg and the phosphate buffer system is added to obtain a pH of 7.4. To this solution varying quantities of dextrose (Kahlbaum's) or sodium lactate may be added to the desired concentration.

I. The respiratory quotient is a direct measure of the relative quantity and kinds of foodstuffs entering into the metabolism of any living substance. The characteristic quotients for each of the basic foodstuffs, *viz.*, carbohydrate, protein and fat, may be derived from the following equations:

Carbohydrate (glucose)

$$C_6H_{12}O_6 + 6O_2 = 6\,H_2O + 6\,CO_2$$

$$\text{R. Q.} = \frac{6 \text{ vol. } CO_2}{6 \text{ vol. } O_2} = 1.0$$

Protein (albumin) empirical formula after Lieberkuhn

$$C_{72}H_{112}N_{18}O_{22}S + 77O_2 = 63\,CO_2 + 38\,H_2O + 9\,CO_2(NH_2)_2 + SO_3$$

$$\text{R. Q.} = \frac{63 \text{ vol. } CO_2}{77 \text{ vol. } O_2} = 0.82$$

Fat (tripalmitin) (Du Bois 1927)

$$C_{51}H_{98}O_6 + 72.5\,O_2 = 51\,CO_2 + 49\,H_2O$$

$$\text{R. Q.} = \frac{51 \text{ vol. } CO_2}{72.5 \text{ vol. } O_2} = 0.703$$

(A) *Respiratory Quotients.*—

Tissue.	Animal.	R. Q.	Experimental variations.
Brain cortex	Human, normal	.98	± .05
	Cat normal, well fed	1.00	± .07
	Cat starvation		
	7 days	1.02	± .05
	8 days	1.00	
	14 days	.99	± .06
	Rat, normal	.98	± .04
	Rat, ethyl alcohol intoxication	.94	± .02
	Mouse, normal	.98	
Spinal cord gray matter	Cat, normal	.99	in plain or .2% dextrose Ringer phosphate.
Cerebellar cortex	Cat, normal	1.00	in plain or .2% dextrose Ringer phosphate.
Meninges	Cat, normal	.86	only one determination.
Testicle	Rat, normal	.78	in plain Ringer phosphate.
		.98	in .2% dextrose Ringer phosphate.
Kidney	Rat, normal	.85	in plain Ringer phosphate.
		.89	in .2% dextrose Ringer phosphate.
Liver	Rat, normal	.77	in plain Ringer phosphate.
Heart ventricle	Rat, normal	.91	in plain Ringer phosphate.

Rat brain cortex 37.5 C.	Ringer phosphate pH 7.4 plain.	Ringer phosphate with 0.2% dextrose.	Ringer phosphate with M/800 sodium lactate.
Respiratory quotient.....	.98	1.04	1.05

Temperature 37.5° centigrade Ringer phosphate solution buffered to pH 7.4.

(B) *Oxygen Consumption.*—Cerebral and cerebellar cortex in the cat were found to consume per milligram of tissue (wet weight) practically identical quantities of oxygen per unit of time observed. Spinal cord gray matter was found to consume approximately $\frac{1}{4}$ to $\frac{1}{5}$ of the amount of oxygen used by brain cortex. The cerebral meninges of the same animal used 1/10 the quantity of oxygen required by brain cortex under similar conditions. The addition of either dextrose or sodium lactate in physiological concentrations stimulated the tissue respiration even though there was no change in the measured respiratory quotient of unity.

The smaller the animal the greater was the oxygen consumption per milligram of its brain tissue. Moreover in animals of the same species—the brain tissue of the younger animal always had a greater oxygen consumption per milligram of tissue (wet weight) than the adult.

Discussion.

Eric Holmes has shown that the different kinds of tissue composing the central nervous system have different rates of oxygen consumption. That cerebral gray matter uses more oxygen than white matter or spinal nerves—also that dextrose addition to the immersion fluid medium increases the oxygen uptake. Holmes further emphasized that this increased oxygen uptake in the presence of dextrose is dependent upon the conversion of glucose to lactic acid and disappears if the conversion is prevented by fluoride.

Moreover using rabbit brain Holmes and Holmes found that the glycogen content of rabbit brain is small and very variable—and therefore it seemed logical that "glycogen plays a comparatively unimportant (or obscure) part in the carbohydrate metabolism of mammalian brain, and that the organ is dependent for lactic acid precursor directly on the glucose supplied to it by the blood."

Both lactic acid and glucose however are absorbed by the brain from the blood in normal, phloridzinized and depancreatized dogs. (Himwich and Nahum and Himwich, Nahum and Koskoff.) The brain does not convert or store these foodstuffs as glycogen. In

depancreatized animals the respiratory quotient of brain remains unity—indicating the utilization of lactic acid—in the absence of insulin necessary for glucose oxidation. The oxidation of combinations of other foodstuffs might yield a respiratory quotient of 1.00, but we must remember that such food substances are present

ADULT WHITE RAT

$\frac{3500}{KO_2}$	1.95	1.86	1.89	1.92
Weight	82.0	83.5	80.0	81.0
Factor	.0238	.0223	.0236	.0237
Fluid	R.Ph. plain	R.Ph. with .2% dextrose	M/800 Na lactate	.2% dextrose plus M/800 lactate
Tissue	.....	....Brain....	.....	.....
60 min.	24.7	41.4	36.9	41.3
120 min.	41.0	80.2	65.2	83.4
60 min.	.587	.924	.87	.98
120 min.	.975	1.79	1.54	1.98

YOUNG WHITE RAT

$\frac{3500}{KO_2}$	1.95	1.87	1.96	1.91
Weight	79.5	79.5	83.0	81.5
Factor	.0246	.0236	.0236	.0234
Fluid	R.Ph. plain	R.P. with .2% dextrose	M/800 lactate	.2% dextrose plus M/800 lactate
Tissue	.....	....Brain....	.....	.....
60 min.	34.3	49.9	43.9	47.0
120 min.	53.2	81.7	76.1	87.7
60 min.	.845	1.18	1.04	1.10
120 min.	1.31	1.93	1.80	2.05

CHART TO SHOW THE OXYGEN CONSUMPTION OF ADULT AND YOUNG RAT BRAIN TISSUE IN DEXTROSE AND LACTATE SOLUTIONS

in very small quantities in the circulating blood. Holmes has shown that carbohydrate is oxidized but only after transformation to lactic acid. Himwich has pointed out the significance of this capability of brain tissue in affording it a factor of safety in "two available sources of energy—glucose or lactic acid." Holmes has demonstrated that insulin diminishes the oxygen uptake of cerebral cortex. I have confirmed this in my work.

Concerning convulsive phenomena the specific rôle of any particular foodstuff is not yet established. I have given cats camphor monobromide convulsions and the excised brain tissue of such animals following a series of severe convulsions still yields a respiratory quotient of unity. Also it has been demonstrated that the brain lactic acid content seems to be directly dependent on the blood glucose level. Holmes has demonstrated no increase in brain lactic acid following thujone convulsions. We all know the convulsions associated with hypoglycemia induced by insulin injection—and since the blood dextrose (the chief brain fuel) and brain lactic acid levels appear to be directly related (*i. e.*, the lower the blood sugar, the lower the brain lactic acid level (Holmes)) it may be possible that the resulting generalized muscular convulsion acts as a protective mechanism to add lactic acid—a food utilized by the brain—to the circulating blood medium. This may be another example of a protective homeostatic mechanism in man.

A biochemical approach to these problems may yield us much of importance.

May I take this opportunity to thank the members of the Russell Sage Institute of Pathology and Miss Frances Marsh for their kind help with this work.

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DISCUSSION.

DR. F. H. PIKE (New York City).—It seems to me that one very significant thing in biochemistry and in the physiology of the nervous system in particular is this demonstration of the nature of the metabolism in the nerve cell. I think that we are apt to forget sometimes that a nervous reaction is a process and that there are changes in matter and energy during that process. I am not saying that things may not be psychogenic, but until it is shown what is the nature of the process which starts up these psychogenic reactions, I don't think we have got so very far along.

The changes in nerve cells during convulsions are matters of interest. It is of interest to learn that the nature of the metabolism, the type of metabolism, is not changed but that its magnitude is changed.

I suppose that since the time of Aristotle, perhaps earlier, medical men have been trying to justify whatever happens on the ground of a protective reaction. The physicist or the chemist is sometimes in doubt as to what things may mean, but in my day no well trained medical student was ever in doubt. He can explain things in terms of final causes.

In the matter of insulin convulsions, I am wondering whether it is the low sugar alone which brings them on. If the analysis is to be trusted, and I may say that the determinations were not so very good, I have seen animals in which the sugar would go to 48 milligrams, below the level at which convulsions appear with insulin, and not show any signs of convulsions or any motor disability. As I say, those analyses at present should be taken with some allowance. We hope to get better analyses. I am rather of the opinion that there is some other element than mere lowering of sugar in the onset of insulin convulsions.

DR. S. BERNARD WORTIS (New York City).—I don't know whether the low blood sugar itself causes convulsions. At any rate we do not see *hyperglycemia* itself causing convulsions. The increase in blood lactic acid that is the result of a generalized muscular convulsion is "foodstuff" utilizable by brain tissue. I think that is important.

It may be that shifts in acid base equilibrium or shifts in water metabolism cause the final setting off of convulsions due to, or associated with, hypoglycemia.

I believe that the methods I discussed, particularly the one of brain arterial and venous blood analysis in conjunction with the Warburg technic, will probably give us much information concerning the biochemical reactions in brain tissue under different conditions of deranged physiological function.

THE NARCOLEPSIES.*

By J. NOTKIN, M. D., and SMITH ELY JELLIFFE, M. D.,
New York City.

In 1926 one of us (Dr. Jelliffe [1]) emphasized the fallacy of nosological classifications in general and pointed out at that time that in narcolepsy we are not dealing with a "disease" *per se* or with a *morbus sui generis* as Gélineau [2] called it, but with a group of symptoms that may occur in a variety of conditions. We know that the narcoleptic symptom-complex has been observed in cases with chronic epidemic encephalitis, it was described by Jakobsohn [3] in multiple sclerosis, by Lhermitte [4] in polycythemia rubra, and by Souques [5] in head trauma. The attacks are known to occur in cerebral neoplasms, in cerebral arteriosclerosis, in cerebral concussions and other affections of the central nervous system.

There are, however, cases in which a most careful examination has failed to reveal definite evidence of involvement of the nervous system, or any other systems of the organism.

In order to throw some light on the problem we have reviewed the cases reported in the literature since 1813. Tabulating the material we found that the cases lend themselves to classification in five definite groups.

In one group we have listed the cases of hypersomnia and cases with sleep attacks in individuals with a definite psychopathological background. Some of the cases of this group belong to the group of psychoneurosis others to schizophrenia or manic-depressive psychosis. Altogether 64 such cases were reported up to 1931.

A second group comprises 29 cases of chronic epidemic encephalitis with sleep attacks alone or with both sleep and cataplectic attacks.

In a third group we have segregated 88 cases with definite involvement of the central nervous system exclusive of group two, or with evidence of unquestionable somatic pathology.

* Read at the eighty-ninth annual meeting of The American Psychiatric Association, Boston, Mass., May 29–June 2, 1933.

In a fourth group we have assembled 30 in which a combination of both narcoleptic and epileptic attacks was described.

Finally, in a fifth group we have gathered 271 cases which we feel may be designated as "cryptogenic narcolepsy" on account of lack of any definite signs, which would indicate some definite organic pathology.

These figures certainly indicate that the disease is not a rarity as the prevailing opinion is, and it may be of interest to mention here that cryptogenic cases were reported by Thümen [6] and by Fricker [7] in 1841, long before the word narcolepsy was coined and the "new and rare disease" described by Gélineau.[2]

The symptom-complex of narcolepsy is too well known to go into details, except perhaps to mention that some investigators emphasize the sleep attacks only while others stress the attacks of loss of tonus, and finally there is a third group of workers who feel that both types of attacks are essential to complete the picture of the so-called true narcolepsy. We may say here that from our experience, only in the cryptogenic group are both types of attacks usually present, while in the symptomatic variety one sees more often one or the other type of seizures.

We have observed both the cryptogenic and symptomatic types. Of particular interest among the latter is a case of general paralysis in which the first symptoms were those of narcolepsy. The patient has been under observation since 1926 and is still an inmate of the Manhattan State Hospital.

One cannot discuss the dynamics of the narcoleptic attacks without considering the mechanisms of the so-called normal sleep. Unfortunately, there is a profusion of theories of the process of sleep and only an enumeration can be made here.

We may mention the theories of cerebral anemia and of cerebral hyperemia. Of interest also is the neurodynamic hypothesis of isolation of the cortex as advocated by Purkinje [8] back in 1846, and the inhibitory neurodynamic mechanism suggested recently by Adie [9] and by Kleitman and Camille.[10] The latter speculated on the basis of Pavlov's [11] studies of conditioned reflexes. Other theories have been offered by Dubois,[12] and Piéron,[13] the basis of which are certain forms of toxicity.

A very intriguing theory is the biological one of Claparède,[14] according to which sleep is a protective measure to avoid exhaus-

tion. According to Claparède sleep assures the integrity of the great functions of the organism.

One must not omit the psycho-analytic theories of sleep as postulated by Freud,[15] Ferenczi,[16] and many others. According to them sleep represents a return to the Nirvana state of the intrauterine life or an escape from a mental conflict.

With the advent of epidemic encephalitis a new anatomophysiological approach was made and the modern theories of normal and pathologic sleep as proposed, for instance by von Economo [17] are well known. It is, however, of interest to recall that as far back as 1890 Mauthner [18] suggested the existence of a sleep center in the posterior wall of the third ventricle.

Many investigators pay particular attention to the endocrine manifestations in narcolepsy and emphasize the relationship of the sleep states to the state of activity of the endocrine apparatus, especially the hypophysis. However, our knowledge of the function of the endocrine system is not as complete as might be and, therefore, it would be premature and speculative to link the mechanism of sleep (both normal and pathological) with glandular processes.

The pathogenesis of affective loss of tonus seen in narcolepsy is just as involved and obscure as that of the attacks of sleep. Here again epidemic encephalitis gave rise to certain speculations and midbrain and hypothalamic changes have been invoked in the explanation of the attacks. It is important, however, to mention here that the manifestations of affective loss of tonus are not always pathological phenomena in a strict sense. Sudden loss of muscular tonus may occur in people who are otherwise not subject to narcoleptic attacks. It is the experience of many observers and of our own that fright or embarrassment may produce in many so-called normal people weakness lasting a moment or so. It was our experience to observe a speaker, who while delivering an address before a gathering became visibly weak in his knees when someone in the audience coughed too loudly. Among the emotional reactions which may influence the tonus of the involuntary system we may quote the occurrence of a release of sphincter control during incontrollable laughter and fright.

As to the pathogenesis of narcolepsy it seems to us that we may be dealing in the narcolepsies with a condition closely related to the epilepsies, recognizing the same pathogenic mechanisms.

Our belief arises from the consideration of the following facts collected from our own material and the ones available in the literature:

1. Paroxysmal nature of the narcoleptic attacks.
2. Occasional occurrence of various types of auras preceding the attack.
3. Hyperkinetic manifestations reported during the narcoleptic attacks.
4. Confusional states reported at times following the attacks.
5. The mixture of both types of attacks—the narcoleptic and epileptic in the same individual.
6. The occasional transition of narcoleptic manifestations into epileptic seizures and vice versa.
7. Epileptic heredity in some instances.
8. Similarly to the epilepsies there are the symptomatic and the cryptogenic types of narcolepsies.

Nevertheless, we feel that the problem is far from being solved. Further studies are necessary. More patients will have to be completely analyzed at the physiochemical, the sensorimotor, and the symbolic levels. Research will have to be carried out at all three levels of the integrated individual.

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DISCUSSION.

DR. S. BERNARD WORTIS (New York City).—Last year Dr. Foster Kennedy and myself had occasion to report only six cases of narcolepsy that were treated with ephedrine. Since that time we have had others. We found in our small series that ephedrine was often more useful in controlling the attacks of cataplexy than in controlling the attacks of sleep. I am well aware of the reports of the Mayo Clinic which showed that the attacks of sleep are very frequently helped. However, so far, we have not been able to confirm that therapeutic result in an equally high percentage of the small amount of material we have. Studies of larger groups of cases are, of course, necessary.

DR. W. G. LENNOX (Boston, Mass.).—Mr. Chairman, I think the authors should mention the matter of therapy and especially ephedrine if they have used this drug in their cases. The Mayo Clinic now have seen some 147 cases of narcolepsy, the majority of which have received ephedrine treatment, and of these the large majority have apparently been very definitely benefited. We would be particularly interested in knowing whether cases that Dr. Jelliffe considered of psychological origin were benefited by the use of ephedrine. We at the present time have one case under treatment who is definitely well as long as he takes ephedrine.

DR. J. NOTKIN (New York City).—If I am not mistaken, Dr. Jelliffe's patients recorded in this paper, were treated by him with psychological methods only. Some of the cases which were seen at the Vanderbilt Clinic have been receiving ephedrine but as these patients disappeared, it was impossible to ascertain the effect of this type of therapy. Apparently ephedrine is efficacious for the sleep attacks and not for the cataplectic attacks. This was also recently reported by Thiele in his monograph.

STUDIES IN ENDOCRINE THERAPY IN EPILEPSY.*

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I. Introduction.

Fashion in medical therapeutics has varied from time to time, especially with such chronic disorders as arthritis, epilepsy, and the psychoses. From year to year periodic popularity has been enjoyed by the doctrines of focal infection, auto-intoxication, allergy, the vitamines, and psychoanalysis. In recent years emphasis appears to have been upon the endocrine glands and their disorders. Moreover, when one considers that well over one-half of our institutional epileptics at the Monson State Hospital present no history of an assignable etiological factor other than heredity (Stein [51]); and that in the family histories of 1000 institutionalized epileptics, who had 6572 parents, brothers and sisters, and children, only 240, or 3.7 per cent of these near relatives had ever had a seizure (Stein [51]), one need not be reluctant to seek eagerly for some possible ray of hope in the still largely uncharted field of the now highly popularized endocrines.

More than empirical grounds offer a basis for such studies. Cobb,[8] Lennox,[38] and Fremont-Smith,[26] call attention to the fact that the emotional element in many cases of epilepsy is obvious as a precipitating factor in seizures; while Cannon,[7] and Cushing,[12] have shown the close relationship between the emotions and the endocrine system. At Monson, one of the most frequent aura is of a visceral nature, described as a peculiar sensation in the epigastrium, accompanied by a rapid heart-beat, a feeling of faintness light headedness or dizziness, fear of impending danger (sometimes of death), with a sinking sensation and sometimes chilliness—a picture that is strongly suggestive of the early stages of traumatic shock as described by Da Costa.[14]

The literature on the subject of endocrine therapy in epilepsy is exceedingly scanty and quickly reviewed. Cushing,[11] Harrower,[27]

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and others, have mentioned the possible relationship between disorders of the pituitary gland and epilepsy. Lisser and Nixon,[39] treated six cases of epilepsy associated with menstrual disturbances (oligomenorrhœa) and reported "striking beneficial results in their menstrual disturbances, obesity, and also in their mental and emotional status. In the five patients under treatment for a long period of time, epileptic seizures either ceased entirely or became far less frequent and much milder."

Harrower,[27] treated over 60 cases of epilepsy, connected with dysovarism, and reported benefit in more than one-half of them, with an apparent cure in 13 cases. He quotes (p. 416) Bisgaard and Madsen, of Copenhagen, as having treated an unstated number of epileptics with parathyroid extract, and reporting that the number of attacks were reduced, and that the psychic condition was improved in three out of five cases.

Unfortunately, until recently most of our information concerning endocrine therapy has reached us, not from the clinics, but through the circulars of the pharmaceutical houses, whose observations are largely confined to the laboratory and to rat units. With the exceptions noted above, endocrine therapy in epilepsy has not proven especially promising thus far.

However, the application of endocrine therapy to disorders other than epilepsy has been gratifying. Thus, we have the use of thyroid extract in myxedema and in cretinism (Dubois[17]), as well as in secondary anemia (Hoskins and Jellinck[33]); cortin (adrenal cortex) in Addison's disease (Hartman, *et al.*[29]; and Rogoff and Stewart[44]); epinephrin ("adrenalin"—adrenal medulla) in surgical shock; pituitrin (posterior pituitary extract) in uterine inertia, hemorrhage and paralytic ileus (Da Costa,[14] p. 190, 724); insulin (pancreatic islets) in diabetes (Harrower[27] p. 411); liver and ventriculin (hog stomach) in pernicious anemia (Murphy[42]); parathyroid in tetany (Collip[9, 10]); pituitary preparations in alopecia (Bengston[2]); posterior pituitary in diabetes insipidus (Hawk,[30] p. 574 and Sprunt[48]); as well as numerous interesting studies by Timme,[53] Stanley,[49] Mazer and Ziserman,[40] Stragnel,[52] and others (Editorial J. A. M. A.[19, 37]). But relative to the psychoses in general, the writings of Bowman,[3, 4, 6] and of Hoskins[32, 34] indicate that at the present time, with the possible exception of thyroid in schizophrenia, there is little to be expected from endocrine therapy in mental disorders.

II. Standards in Endocrine Therapy.

Hoskins and Sleeper [35] recently reported the result of four years of endocrine studies on dementia præcox. They observed that 14 out of 16 schizophrenics improved on thyroid therapy, that haphazard treatment with endocrine preparations was useless, inasmuch as only those cases in which endocrine treatment was specifically indicated showed any tendency to improve under the treatment, that relatively large doses (60 to 75 grains of B. & W.—equivalent to 12 to 15 grains of the desiccated gland R. & C. or P. D.) of thyroid treatment was tolerated and that when the treatment was discontinued, the improvement also tended to disappear, most of which observations are corroborated by the present study.

In addition to these pertinent and valuable findings, these writers, insist that negative results in endocrine therapy are usually not conclusive. They write, "Before one can render an adverse decision, four principles must be shown: First, that the gland substance selected was the one that was indicated in the individual case; second, that a potent preparation was used; third, that the dosage was adequate; fourth, that treatment was continued for a sufficiently long period of time."

These postulates, as reasonable and inclusive as they are, are not as simple of fulfillment as they appear. For example, there are at least 20 gland or tissue products that are listed in the catalogues of the various pharmaceutical houses as having one or more internal secretions. These tissues are arranged alphabetically in Table I.

TABLE I.

List of Alleged Endocrine Tissue Substances.

1. Brain.	11. Pineal gland.
2. Bone marrow.	12. Pituitary body.
3. Duodenal substance.	13. Placenta.
4. Kidney.	14. Prostate.
5. Liver.	15. Spleen.
6. Mammary gland.	16. Stomach.
7. Myocardium	17. Suprarenal body.
8. Ovary.	18. Testicle.
9. Pancreas.	19. Thymus.
10. Parathyroid.	20. Thyroid.

Barker, Hoskins and Mosenthal (Hawk,[30] p. 558), in their schematic chart of the endocrine system, omit brain, bone marrow,

kidney and myocardial substance, but, add the carotid gland and coccygeal body. (See also Engelbach.[20])

From these 20 gland tissue substances, I have been able to find more than 40 known hormones and antihormones or chalones.

Besides the well known preparations of the endocrine glands listed in Table I, desiccated for oral use and extracted for hypodermic administration, the following preparations in common usage, selected from the pharmaceutical catalogues, merit a few words of explanation (Table II).

TABLE II.

A Partial List of Endocrine Preparations in Common Use.*

1. *Liver:* Anabolin, (Har.); Heparhemin, (Har.); Heparnucleate, (Har.); recommended for the anemias. Liver Extracts, (All).
2. *Ovary:* Ovacoids, (R. & C.), oral; Ampacoids, (R. & C.), hypo; Estrogen and Theelin †, (P. D.); Endo-Luteum, (Har.); Lipo-Luteum, (P. D.); Luthorm, (Upj.); Corpus Luteum, (All); from ovarian follicle; also Progynon (Schering), follicular hormone for oral or hypo, recommended for menstrual disorders and accompanying states, *i. e.*, sterility, infantilism, menopause. (See reports of Stragnel,[52] and Rock.[48])
3. *Pancreas:* Panacoids, (R. & C.); Panteric Compound, (P. D.); Islands of Langerhans, (Ab.); Pan-Secretin, (Har.); all from pancreas with or without bile salts, duodenal substance, or cathartics; recommended for all forms of intestinal indigestion, and diabetes mellitus.
4. *Parathyroid:* (All); Paroidin, (P. D.); Paracalcin, (Har.); Parathormone, (Lil.); recommended for tetany, gastroenteritis, spasmophilia and epilepsy.
5. *Pineal Emplets:* (P. D.), enteric coated, desiccated Pineal body; recommended for juvenile mental retardation.
6. *Pituitary Body:* Whole, anterior, or posterior lobes, desiccated, (All):
   A. *Posterior pituitary:* Pituitrin, Pitressin, Pitocin, (P. D.); recommended for classical uses of pituitrin.
   B. *Anterior Pituitary:* (All); Antuitrin S. (P. D.); Apestrin, (Har.); Accretin, (Har. Anterior Pituitary with Thymus); Follutein (Sq.); recommended for stimulation of growth, menstruation, and sexual development.
7. *Prostate:* Ampacoids, (R. & C., hypo); Prostate Compound, with Leydig cells, (Har.); recommended for "male menopause," neurasthenia and sterility.
8. *Stomach:* Ventriculin, (P. D.); recommended for pernicious anemia.
9. *Suprarenals:* Adrenalin, (P. D.), Suprarenin, from medulla; recommended for classical uses (shock, etc.) Cortin, (P. D.); Adreno-Cortin, (Har.); recommended for addison's disease.

10. *Testicle:* Testacoids, oral, Ampacoids, testicle, hypo, (R. & C.); Orchic Substance, (All); recommended for sterility.
11. *Thyroid:* Thyracoids, (R. & C.); Thyroid Extract, (All); Thyroxin, active principle of thyroid gland (is crystalline trihydrotriiodo-alphaoxybetaindol, containing iodine) for increasing metabolism. (Timme,[54] p. 1165.)
12. *Mixed Glands:* (in addition to the common combinations of all glands with the addition of pituitary and thyroid as activators):
    A. *Virilogen,* (G. W. C.) anterior pituitary, suprarenal cortex, lymph, brain, spinal cord, testes, and thyroid; recommended for lowered virility and sexual neurasthenia.
    B. *Tonicine,* (R. & C.), gonads of either sex with strychnine and Sod. glycerophosphate; Tonic for sexual asthenia.
    C. *Protonuclein,* (R. & C.), a formula of mixed glands: Brain, thyroid, spleen, suprarenal, thymus, pancreas, salivary, lymph and pepsin; for neurasthenia.
    D. *Incretone,* (G. W. C.), thyroid, whole pituitary, ovary, and testes; general tonic.
    E. *Mammogen,* (G. W. C.), whole pituitary, corpus luteum, and placental substance; recommended as a galactagogue.
    F. *Kinazyme,* (G. W. C.), whole pituitary parathyroid, pancreas, liver, spleen, and calcium phosphate; recommended for metabolic disorders, tuberculosis and malnutrition.
    G. *Zenner's Mixed Gland Compound,* (Zenner), contains thyroid, suprarenal and testicle; general tonic.

* *Abbreviations.*—1. All—All houses, or most of the pharmaceutical houses. 2. Ab.—Abbot. 3. G. W. C.—G. W. Carnrick. 4. Har.—Harrower. 5. P. D.—Parke Davis. 6. R. & C.—Reed & Carnrick. 7. Upj.—Upjohn. 8. Sch.—Schering. 9. Lil.—Lilly. 10. Sq.—Squibb.
† Obtained from the urine of pregnant women.

Thus there is Prolan A which stimulates the ovarian follicle to maturation, and to produce the hormone Theelin which is found in excessive quantities in the urine of pregnant women, the presence of which constitutes the basis for the now popular Ascheim-Zondek test for pregnancy (Hawk,[30] p. 571). This is marketed as Theelol (P. D.), and Follutein (Sq.). Prolan B. hastens luteinization after the follicle has ruptured (Evans [22, 23]). Harrower [27] presents Apestrin as the estrus-inducing hormone of the anterior pituitary, and its chalone or antihormone Aplutin, which favors luteinization and is similar to the corpus luteal hormone. There are in addition, according to these authors, a growth promoting hormone, a thyreotropic hormone that stimulates the epithelial growth in the acinæ of the thyroid gland and causes a disappearance of the colloidal content, a lactogenic hormone that stimulates the mammary glands,

a diabetogenic hormone, an adrenalotropic hormone and a gonadotropic hormone. Moreover Bauman and Hunt [1] call attention to the synergistic action of both the anterior and posterior lobes of the pituitary gland in producing specific dynamic action in hypophysectomized rats, which probably explains the efficacy of whole pituitary gland in the present and other studies (Bengston,[2] Foster & Smith,[25] and Harrower [27]).

From the ovary there are also several hormones that have been isolated. Thus for menstrual difficulties we have our choice of the dried whole ovary, ovarian follicle, and corpus luteum. In addition there are hormones from the placenta, and the sex stimulating hormones of the anterior pituitary. Unfortunately, the clinical results from most of these preparations do not measure up to the claims and expectations set for them by their pharmaceutical houses, nor are they as startlingly successful as one would have us believe (Rock [43]); although Evans and Long, Smith, *et al.* (quoted by Hawks,[30] pp. 573-574) and others have shown what can be accomplished by transplants and injections of the pituitary gland in laboratory animals.

Even the thymus is apparently not free from sin, since Riddle found that birds with small thymi were producing eggs in which the shells were soft; and oral administration of ox thymus corrected the disorder. So we have a new hormone "thymovidine" (Hawks,[30] p. 575).

An incomplete list of the common available endocrine preparations is given in Table II.

As though the picture were not already sufficiently complex, Falta-Meyer,[24] Harrower,[27] Hawks,[30] Evans,[22] Cushing,[13] and Timme [53] report that there is also a considerable amount of reciprocal complementary and inhibitory activity between various combinations of the endocrine glands. For example, the thymus is antagonistic to the gonads, atrophying after childhood to permit growth and maturation (Harrower [27]). The suprarenal cortex is antagonistic to the thyroid, while the suprarenal medulla has an inhibitory effect upon the pancreas (Falta-Meyer [24]). Hypophysectomy in the rat produces a characteristic inhibition of growth in young animals, loss of weight in mature animals, atrophy of the thyroids, suprarenal cortex (Evans [22]), and sex glands (Smith [47]), so that reproduction becomes impossible owing to the occurrence

of amenorrhœa in the female or of impotence in the male (Cushing[11]). (*Cf.*, McGee's testicular injections into capons.[18])

The mammary gland antagonizes the ovary in order to delay ripening of the follicle during periods of lactation and pregnancy (Harrower[27]). The corpus luteum also inhibits ovulation and estrus since its removal allows these phenomena to take place (Hawk[30]). Castration lowers the metabolism of the body while cortin therapy raises it in adrenalectomized rats (Hartman[28]). Hypophysectomy ameliorates diabetes produced by ablation of the pancreas (Evans[22]).

Adrenalin stimulates the liver to produce more glycogen and ultimately a glycosuria, but the glycosuric action of adrenalin which is diminished after extirpation of the thyroid, is not diminished on simultaneous extirpation of the parathyroid and may even be somewhat intensified. Also extirpation of the thyroid raises the assimilation limits for carbohydrates and reduces the albumin exchange during fasting. Simultaneous extirpation of the pancreas and thyroid produces a diabetes which, however, pursues a milder course to the extent that the albuminous destruction is not so high and the diminution in weight does not progress so rapidly as in the diabetes produced by extirpation of the pancreas alone. Therefore, there has occurred a diminution of an otherwise increased metabolism (Falta-Meyer[24]).

Hence, polyglandular dystrophy is an established fact and polyglandular therapy is, therefore, a rational procedure (Timme,[54] p. 1191).

To maintain as some do (Rowe[45, 46]) that only one gland is likely to be affected at any given time is like insisting that in any given illness only one organ in the body can be affected at a time. It appears, therefore, that the doctrine of therapeutic attempts—for that is what now comprises most of modern endocrine therapy—with only one gland at a time has no more rationale than the treatment of, say a cardiac, with only one of the customary and valuable therapeutic procedures of rest, digitalis, sedatives, stimulants, diuretics, or venesection.

The general clinical appearance of disorders of the thyroid, parathyroids, pituitary, adrenals, gonads, and pancreas, and their systemic effect on the pulse, blood pressure, metabolism, and emotional states in such conditions as goitre, myxedema, cretinism,

acromegaly, gigantism, eunuchoidism, diabetes, Addison's disease and menstrual disorders are too well known to need enumeration here. They serve merely to indicate still further the close relationship between the autonomic and endocrine systems, and the metabolic and emotional states (Cannon,[7] Cushing[12]).

Nor should such a complex system be surprising when one reflects that there exists in the body many other elaborate systems of stimulation and counter-stimulation among its various enzymes. Thus acid chyme from the stomach on entering the duodenum changes prosecretin in the succus entericus to secretin which passes into the blood stream, thence to the pancreas stimulating the flow of pancreatic juices containing the enzymes, trypsin, erepsin, steapsin, amylopsin and prokinase (Hawk[30]). Prokinase in the pancreatic juice changes to enterokinase on coming in contact with the succus entericus, and the enterokinase activates the tryptic enzymes. Cholecystokinin acts similarly upon the gall-bladder (Ivy, *et al.*[36]). Another example is the process of blood coagulation, wherein prothrombin is held in check by antithrombin, the latter being liberated when thromboplastin is freed during hemorrhage by disintegrated blood platelets so as to combine with the antithrombin. Prothrombin is then activated by calcium to change fibrinogen into fibrin to form the blood clot. (Hawk,[30] p. 384.)

A list of the action of the body hormones, even if it were complete would be a lengthy study to say the least; while the number of possible combinations is literally incalculable.

So much for the task of selecting the appropriate gland to use, assuming of course that we could determine clinically whether a given case of hypogonadism with infantilism, for example, was due to a disturbance of the pituitary gland before or after puberty, and whether this disturbance was of a hypo- or hyperactive nature, or to a disorder of the gonads themselves. Or, as another illustration, whether a given case of dysmenorrhœa was due primarily to an ovarian insufficiency, to thyroid inadequacy, or to a deficiency of one or more of the several hormones of the anterior pituitary lobe. Some guidance can be had by the tables of Trumper and Cantarow,[55] giving an outline of chemical diagnostic features of the various endocrine disorders including differences in cholesteremia, glycosuria, metabolism, calcemia, phosphatemia and glucose tolerance; but, unfortunately, the clinical standards now avail-

able for the proper diagnosis of the various endocrinopathies are by no means uniform, and certainly they are not simple.

The second postulate of Hoskins, *viz.*, that a potent preparation must be used, would appear to be self-evident. But if, on the one hand, one is to judge from the literature of the pharmaceutical houses—which reach more doctors than do many of the accredited journals—they all produce nothing but potent preparations; while, on the other hand, the reports on the clinical efficacy of the majority of the various endocrine products are conflicting to say the least. The one uniform opinion is that preparations that are put up for hypodermic use are inert if given by mouth as also are the isolated hormone extracts from the several glands. However, when one reflects that the hypodermic preparations of most of the various endocrine products commonly cost between 30 and 60 cents or more for each injection; and that one or more injections daily is the recommended dosage, over a period of months or years, he need not be slow in recognizing that the expense, which even for this small study was well over one thousand dollars, is a major objection to the prolonged use of hypodermic preparations. Inconvenience, requisite professional administration, and the frequent occurrence of pain at the site of inoculation are other common objections. Moreover, according to Hawk [30] the oral route is apparently unsatisfactory only for the isolated hormones; for there is much in the present and other studies (Bengston,[2] Timme [54]) to indicate that like liver and thyroid, the desiccated preparations of the whole pituitary and suprarenal gland can be given orally with definite clinical results in the form of alterations in peristalsis, pulse, blood pressure, weight, body measurements, metabolism, and general well-being (and sometimes menstruation). Doubtless, however, the dosage is higher than by the hypodermic route.

Concerning the third postulate, I know of no way of proving when an adequate dosage has been reached. Thus, one patient will tolerate a whole cubic centimeter of pitressin, while another fainted on three or four minims. One adult patient vomited and became dizzy and excited on one half a grain of thyroid, while a five year old cretin, who had accidentally swallowed seven and one-half grains of the gland (30 one-quarter grain tablets) at one time, reacted no more than by becoming pugnacious, and picking a quarrel with his older brothers and sisters. Two patients de-

veloped a "pituitary headache," with slowed pulse, nausea, and malaise on a grain each of thyroid and whole pituitary by mouth,* while a dozen others reacted not at all, except by loss of weight and diminished constipation, to doses that were from three to five times that amount.

Lastly, as to how long the treatment must be continued in order to show whether or not the preparation was effective, that too, is difficult, for the best opinion in the treatment of epilepsy is that the longer the interval between any given seizure and its successor, the better the chances for preventing a recurrence. This means that the treatment of epileptics whether it be with endocrine or any other preparations, like the use of insulin in diabetes, must be continued indefinitely.

III. Purpose.

In view of the difficulties accompanying any clinical study of the endocrines and their disorders most of this program was laid along empirical lines. The purpose was to determine: 1. Whether there was any specific endocrine disorder that appeared to be responsible for the production of epileptic seizures. 2. Whether epileptic patients with accompanying clinical features of an endocrine disorder could be helped by treatment with any of the available endocrine preparations. 3. Whether such patients, if clinically helped from the endocrinological viewpoint, would also show a reduction in the frequency or intensity of their seizures. 4. Whether any of the available endocrine preparations had a specific effect empirically upon seizures *per se,* regardless of the presence or absence of accompanying disorders in the endocrine systems of the patients tested.

IV. Procedure.

The studies in endocrine therapy in epilepsy have been carried on during the past two years at the Monson State Hospital for epileptics in Massachusetts. Sixty-eight epileptics, eight of whom were males, were studied for periods varying from 6 to 80 weeks depending upon the degree of co-operation and frequent interruptions by other illness, status, and absences on home visits.

* This was overcome by reducing the thyroid which apparently acts as a catalyzer.

Seventy-five non-epileptics, including some nurses and attendants, 35 of whom were males, have been under observation with endocrine therapy (mostly for specific endocrine complaints as obesity, asthenia or dysmenorrhœa) either directly or indirectly through the co-operation of their own physicians in this and other out-patient clinics (Monson State Hospital, Springfield Hospital Child Guidance Clinic, Springfield, Mass., and Public Health Center, Oakland, Calif.) during the past four years. These have been used as a basis of control; although in the strictest sense any accurate and scientific control in such a study is impossible due to individual differences in physical, emotional, social and other states, as well as to the impossibility of accurate endocrine diagnoses in general. However, the same preparations were used for both sets of patients.

One case of narcolepsy, a boy of 17 is included in the study. Female epileptics who had had their first seizure during adolescence, and subsequent seizures mainly in relation to their menstruation were selected as far as possible; partly because this class gave an opportunity each month for frequent periodic checking up on the efficacy of the therapy (in contrast to patients who sometimes had no convulsions for many months at a time) but also, because those patients who have had their first seizures during adolesence stand a far better chance of recovering than those with the onset of seizures before or after that period (Hodskins [31]). A smaller group was selected only because these patients were having large numbers of seizures. This was for the purpose of testing the efficacy of the preparations upon the seizure *per se*. In general, patients with frank metabolic disorders were given preference because a check on the weight, as well as pulse, blood pressure and basal metabolism also afforded some indication of the efficacy of the treatment, most of which medication was administered orally.

Basal metabolic tests were taken whenever possible; but were not used as an index for therapy because, like pulse, blood pressure (Cannon [7]), sugar tolerance (Rowe [46]) and peristalsis the metabolic rate tends to vary with the emotional status of the individual tested (Hoskins,[32] Bowman [5]). For this reason, and the difficulties of obtaining the test—especially in the controls whose finances frequently rendered it impossible—the standards for gui-

dance used were: pulse, blood pressure, weight, peristalsis (*i. e.*, usual bowel activity), menstruation, and general well-being. Even in the matter of weight the emphasis was laid, according to accepted standards, upon the quality and distribution of the fat rather than upon the quantity in pounds (Cushing,[11] Rowe, *et al.*,[46] Timme [54]).

Single gland therapy was used in the beginning in practically every case until several months of treatment indicated no clinical therapeutic effect; after which, thyroid or whole pituitary or both was usually added.

Preparations of whole pituitary, suprarenal, and thyroid gland purchased from Parke Davis, Lilly and Armour were used at first. Later, a large supply of Progynon and of Thyreotropic Hormone was made available through the courtesy of Dr. G. Stragnell of Schering & Co., of New York and Germany. But, the bulk of this research was made possible through the continued co-operation of Dr. H. S. Baketel and the research department of Reed and Carnrick of New Jersey, from which laboratories the following preparations were used: whole pituitary, anterior and posterior pituitary, thyracoids, suprarenal, corpus luteum, ovacoids, testacoids, ampacoids (prostate, testicle, and ovary respectively, for hypodermic use), panacoids, pancrobilin and the special formulæ No. 104 and No. 105 containing whole pituitary, thyroid and hormones of the respective male and female gonads. Most of these preparations have also been used on the controls and all were for oral administration except Ampacoids, Progynon and Thyreotropic Hormone, which were for hypodermic use. In addition, Amniotin, Estrogen, and Theelin have been used on some of the controls with menstrual disorders.

V. Results.

1. *Metabolism.*—Basal metabolic rates in the epileptics tended to be subnormal on first readings at the beginning of treatment. Of 60 metabolic rates which have been done (58 of which were included in this group under treatment, and 49 of which were females), only 13 were above zero, six were higher than + 10, and three were higher than + 20. Thirty were below zero. Of these, 14 epileptic patients had a metabolic rate below — 10, and

two were below — 20. So that the general tendency, at least in this group, was for lowered metabolism. These findings bear out the reports by Damon [15] and Bowman [5] of a generally lowered basal metabolism in epileptics.

Thirty epileptics had two or more tests; and 14 of these showed lower readings on subsequent examination, despite thyroid treatment, while only 15 showed a higher rating. The changes ranged from 5 to 20 per cent.

2. *Blood Pressure.*—Blood pressures among the epileptic group tended to be slightly lower than average for age; while pulse rates tended to be slightly higher than average. A study of blood pressures made at the hospital on 350 males and 248 females, and standardized by the method of Faught (Prudential Life Insurance Manual, 1932) reveals the following:

TABLE III.

BLOOD PRESSURES OF 598 EPILEPTICS.

Classification (Faught).	350 males.		248 females.		Total (598).	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
1. Normal	192	55.0	131	52.6	323	54.0
2. Below normal	140	40.0	90	36.3	230	38.5
A. 10-20 per cent below	46	13.3	57	23.0	103	17.2
B. Below 20 per cent..	94	26.7	33	13.7	127	21.3
3. Above normal	18	5.0	27	10.9	45	7.5
A. 10-20 per cent above	4	1.0	17	6.9	21	3.5
B. Above 20 per cent..	14	4.0	10	4.0	24	4.0

3. *Menstruation.*—Menstruation responded in a variety of ways. On Progynon (Schering's estrus-inducing follicular hormone), five epileptics and four controls noted a complete cessation of their menses; while three other epileptics (Cases 14, 19, and 38) noted a decided increase in the severity and frequency of their convulsions, comparable to that which is noticed at the regular menstrual cycle. One control (Case 13), an involutional melancholia near the time of menopause was treated promptly at the onset of her illness and failed to respond in any way to 75 rat-units of Progynon injected daily for eight consecutive days; while, another woman (Case 128), with extreme obesity and amenorrhœa of 18 months beginning one year following the birth of her second child, failed to respond to repeated injections of Progynon for

three successive months. However, in this last case, after the addition of whole pituitary, grains two, and thyroid, grains one, three times daily for two more months, menstruation was finally re-established, and the adiposity reduced.

Other cases of amenorrhœa and of dysmenorrhœa, as well as two cases of menorrhagia, likewise failed to respond to injections of either Progynon or Thyreotropic Hormone (Schering's anterior pituitary thyroid-stimulating hormone). Nor did they respond to the oral administration of Corpus Luteum. (R. & C.)

A mixture of desiccated whole pituitary gland gr. one-third, thyroid gr. one-eighth, and whole ovary gr. one, known as special formula No. 105 was made up by Reed & Carnrick, and seemed to offer some promise at first. One girl (Case 5) while on this mixture, went through her first catamenia in four years without an accompanying convulsion; but, had a seizure some 10 days later. Another girl (Case 51) skipped two successive menstrual periods without an accompanying convulsion for the first time in over a year. However, she had in times past skipped as many as two successive months without a seizure, so that coincidence could not be ruled out. Neither of these two girls repeated the procedure on either this or any other treatment. One patient (Case 38) who had shown an increase of seizures on Progynon, also had a similar but less marked increase while on the special formula No. 105 but did not have an increase of seizures over her normal routine of convulsions while she was on thyroid and pituitary without the ovary.

A similar preparation special formula No. 104, of whole pituitary and thyroid with five grains of orchic substance instead of ovary was also made up by Reed & Carnrick, and proved inert in eight male epileptics; but was effective in several control cases of cryptorchidism seen at the Springfield Hospital Child Guidance Clinic for complaints of habit spasms, temper tantrums, and similar evidences of instability. It was also effective in the case of narcolepsy (*q. v.*, below). (As in the case of No. 105, later observations tend to show that the favorable effects are obtained from the pituitary and thyroid content, rather than from the gonad.)

4. Concerning the rest of the preparations used, few things of note stand out: parathyroid (gr. one-tenth), with and without calcium lactate (gr. 10), even in large doses (six to nine times daily),

was without effect on seven patients, including one with myoclonus (Case 31). Panacoids (R. & C.) apparently improved pancreatic digestion, and relieved several cases of constipation, but the relief lasted only while they were taking the preparation. The mother of one of the control cases noted a disappearance of halitosis in addition to a relief from constipation in her child, while on Panacoids. Several other controls have since corroborated this observation.

The use of desiccated whole suprarenal gland offered some interesting possibilities. Seven epileptics were given doses of from two to eight grains immediately following a seizure. In five of these there was noted a shorter period of convalescence from the usual post-convulsive debility, headache or malaise and disturbance, so that the patients were able to be up and about their usual routine within a few hours instead of a day or longer. One epileptic (Case 5), who gave every indication of an impending seizure, according to nurses who were well acquainted with her for years, and whose own observations are reliable, "aborted" her convulsion on three doses (of four grains each) of suprarenal gland (a similar result was obtained with adrenalin *q. v.*, below). However, she also had her convulsion several days later; and coincidence could not be ruled out since the performance was never repeated. In three others (Cases 28, 7, 11) to whom the gland was fed on the first signs of an aura, the impending seizure came according to schedule, but apparently left the patients with milder sequellæ, so that they "didn't mind it so much." Steady daily doses of suprarenal gland failed to affect the convulsive program in any patient, and only small doses (two grains, three or four times daily) were tolerated without digestive disturbances.

Among the controls as well as the epileptics, a common report was that a few doses of suprarenal gland (grains two) taken by mouth at the beginning or during some respiratory infection, or when exhausted by emotional strain, worry, insomnia or physical fatigue, caused a prompt return of general pep and well-being within a few hours. Larger doses or prolonged use caused digestive disturbances ("heartburn," diarrhœa, flatus) and nervousness, with an increase in pulse rate. Small doses of thyroid (gr. one-fourth to one-half) acted similarly.

5. Adrenalin, 1/1000 solution was used in only three epileptics; no seizures were precipitated, even on two and one-half cc. injected within a period of 40 minutes in Cases 49 and 50; but, on the contrary in Case 5, whose observations were corroborated by the attending nurses, on two successive occasions, an impending seizure was aborted for several days. (Two one-half cc. doses were injected subcutaneously five minutes apart, at the first appearance of definite signs of an aura.) The studies with adrenalin are to be extended.

6. The thyroid gland (in doses varying from .3 to 15 grains daily) was given independently to 35 epileptics for a varying period of time and 13 of the 35 improved in general health. Forty-six patients have received thyroid in combination with other medication; and 34 of them showed an improvement in nutrition, digestion, bowel activity, and general well-being. Inasmuch as lowered metabolism is common in this group, the improvement was probably due to the thyroid content of the mixed formulæ; since only suprarenal, of all the other preparations that were used, afforded anything like similar improvement, when used alone. However, the improvement on thyroid was more lasting, and affected a larger proportion of patients than did suprarenal gland.

Frequently the pulse rate, as well as the metabolism tended to be lower after thyroid medication instead of higher as would be expected. This serves to remind us that there is also a clinical hypothyroidism that is marked not by obesity or myxedema, but by asthenia, underweight, bradycardia, and periods of "vagotonia" (Eppinger and Hess [21]). In this type of case, the precipitating factors of the fatigue seem to be infection, anxiety and emotional excitement; while digestive disorders, especially flatus, "heartburn," and either sluggish or frequent bowel movements, are commonly noted. The type is common to both epileptics and controls. In the former, if there is an aura it is usually of an epigastric type; while in the latter the customary label is neurosis or gastritis nervosa. In both epileptic and control this type does well on very small doses of thyroid gland (gr. one-tenth) given over a limited period of hours or days, at fairly frequent intervals. Frequently too, small doses of whole suprarenal gland by mouth appear to have a similar effect, bearing out the observations of Falta-Meyer [24] that the suprarenal medulla and the thyroid glands are supportive

to each other. Apparently the thyroid acts like a catalyzer to the other glands, as well as to the body metabolism as a whole.

7. Three cases of dermatitis, chronic eczematous lesions that had defied expert skin care for years, cleared up quite unexpectedly during the course of treatment, presumably from the thyroid content of the régime. Two of these were controls who were being treated for something quite distinct from epilepsy. One of the latter, however, suffers a relapse whenever she discontinues her treatment; while the other two have remained symptom-free for over 20 months.

8. A group of eight male epileptics with frequent seizures showed no effect upon seizures or upon general well-being from any of the preparations used, except one with obesity (Case 29), who is losing weight rather slowly (on No. 104 at first, and later on pituitary and thyroid) but continues his convulsive program unchanged.

9. One case of narcolepsy, a boy of 17, failed to respond to the régime of ephedrine sulfate (up to 4½ grains daily) so enthusiastically described by Doyle and Daniels.[16] There was likewise no improvement on Zenner's mixed gland compound prescribed by his local physician, until huge doses of it (20 tablets daily began to produce some abatement of the somnolence. However, there was noted a gradual but marked reduction in somnolence on a combination of ephedrine sulfate (gr. three-fourths *q. i. d.*) and the special formula No. 104 (R. & C.) referred to above. The results from this therapy support the findings of Serejiski and Frumkin (quoted by Myerson,[14] p. 233). Offsetting this, however, were marked outbursts of temper that became worse as dosage was increased and as somnolence vanished, and occasional attacks of vomiting. Tumor was ruled out; but the "only child" complex, and other social and emotional complications made treatment extremely difficult. Prompt relapses were noted on two occasions when treatment was discontinued for a few days.

VI. Summary and Conclusions.

1. The intriguing possibilities of endocrine therapy in epilepsy are evidenced by the close relationship between metabolism, the endocrine glands, the autonomic nervous system, and the emotions, all of which are commonly affected in epileptics (Section I).

2. A review of the literature indicates wide discrepancies between alleged standards for the diagnosis of endocrinopathies, as well as between divers reports of clinical trials with various hormones. Moreover, dozens of hormones and innumerable combinations of internal secretions from a score of endocrine tissues (Tables I and II) have been occupying the attention of more workers with rat units in the laboratory than of clinicians. Because of this, our present state of knowledge of the endocrine system does not permit a judicious clinical use of most of the available supply of endocrine preparations; and, therefore, Hoskins' postulates (Section II) are at present impossible of fulfillment.

3. Despite these handicaps and the expense, as well as the variance of clinical trials with laboratory experience, the continuation of empirical attempts with selected endocrine preparations is justified not only by the relative failure of medicine in the treatment of epilepsy, but also by observations made in the present study.

4. The results of therapy with a selected group of endocrine preparations (Section III) on 68 epileptics, one narcoleptic, and 75 non-epileptic controls of both sexes are given in Section IV. However, a scientific control is impossible due to fundamental differences in the personality, and in the physical and emotional states between epileptics and non-epileptics. Nevertheless, the same preparations were used for both groups. A comparison of the convulsive record of the same patient before and during treatment offered the best basis of control, under the circumstances.

5. None of the endocrine preparations that were used in this study were specific for convulsions—neither curing them in the epileptics, nor causing them in the controls. However, there is some evidence that, in a few cases at least, an overstimulation of the ovaries (Progynon and whole ovary both alone and in combination) may be indirectly provocative of convulsions.

6. The majority of cases that received thyroid substance, either alone or in combination with other glands, showed definite clinical improvement in metabolism, bowel activity, and general well-being. This was more true of those who had been on treatment for longer periods of time, as was the case in most of the controls. The observations of Hoskins and Sleeper,[85] on a tendency for the improvement to subside when treatment with thyroid in schizophrenia is stopped, is substantiated by these studies. This is probably

explained by the subnormal basal metabolism in both epileptics and schizophrenics.

7. Blood-pressures, like metabolism, tended to be subnormal (Table III); and there is some evidence that in many cases of hypotension dried suprarenal gland by mouth, as well as thyroid, will raise the pressure from 10 to 30 mm. and maintain the rise as long as medication is continued.

8. The best results were obtained in both epileptics and controls with pituitary, thyroid and suprarenal; but many years of continued observation will be necessary before much of value will be known about this phase of the treatment of epilepsy. In the meantime polyglandular dystrophy is more commonly the rule than the exception, and pluriglandular therapy is more efficacious than single therapy except in treatment with thyroid.

9. Endocrine therapy should be but one part of the general therapeutic program; and does not deserve consideration to the exclusion of sedatives, dietary restrictions, gastro-intestinal regulation, psychotherapy, and the usual routine hygienic measures. Inasmuch as these measures were used where indicated throughout the present study, it is perhaps unreasonable to place too much emphasis upon the virtue of the endocrines *per se;* for, as Cushing[13] recounts, toxic goitres were successfully treated by sedatives, psychotherapy, and sometimes cervical sympathectomy before thyroidectomy became fashionable in surgery. Thus one epileptic, who developed what the psychoanalysts would call a "positive transference" to the examiner, was found to be losing weight and thriving on a self-imposed reduction diet even before her medication was ordered. In the meantime, the predominance of epigastric auræ and of emotional etiological factors in many epileptics seems to focus attention upon the epigastrium and cœliac ganglia, as well as the autonomic nervous system as a whole.

10. There is no known endocrine disorder that appears, at this time, to be specifically responsible for the production of epileptic seizures.

11. Patients with obesity and constipation offer the best prospects for improvement with oral administration of thyroid and whole pituitary gland in combination; while patients with menstrual disorders are most resistive to treatment with either oral or hypodermic preparations of the commonly advertised estrus-inducing hormones, as well as with thyroid and pituitary.

12. Patients who improved in general health while on treatment, and the majority of them did, did not show any reduction in the frequency or in the severity of their seizures; but did show a lessening of the post-convulsive debility, headache and weakness, and also a marked shortening of the post-convulsive period of convalescence.

13. Patients in both groups who were under observation for longer periods of time showed a better response to therapy, which probably explains the higher proportion of improvements in the controls. Some noted a lengthening of their aura.

14. It is reasonable to expect that if the clinical improvement in the metabolism, gastro-intestinal function, and general well-being of these epileptics can be maintained for a period of several years at least, the convulsive threshold may also rise to the point of overcoming their seizures.

The research is being continued.

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THE CHANGES IN THE CONCENTRATION OF INORGANIC CALCIUM AND PHOSPHORUS DURING CONVULSIONS OF EXPERIMENTAL ORIGIN, IN CATS, BEFORE AND AFTER THYROPARATHYROIDECTOMY, WITH AND WITHOUT BROMIDE THERAPY.*

By HELEN C. COOMBS, Ph. D., DONALD S. SEARLE, Ph. D., and F. H. PIKE, Ph. D.

I. The general statement of the question.
   A. The general phenomena of a convulsion—muscular, cardiovascular, visceral, basal metabolism (Damon), petechial hemorrhages, chemical.
   B. The various hypotheses on the origin of convulsions.
      1. Toxic origin.
      2. Physical origin.
      3. Circulatory origin.
   C. The effects of endocrine and other bodily conditions upon the incidence of convulsions.
   D. The experimental means of inducing convulsions of each of these three types.
      1. Camphor or absinth.
      2. Electrical excitation of the cortex.
      3. Occlusion of the head arteries.

II. Experimental Technique and Procedure.
   A. Removal of the thyroparathyroid combination—general deportment, care of animals, length of life of animals previously fed bromides.
   B. Technique of experimental elicitation of convulsions.
      1. Camphor or absinth.
      2. Electrical excitation of the cortical motor area.
      3. Occlusion of the head arteries.

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III. The Experimental Results.
  A. The general reaction of animals to the different methods of eliciting convulsions.
    1. Summary of the observations on control animals.
      i. Camphor or absinth.
      ii. Electrical excitation.
      iii. Occlusion of the head arteries.
    2. The reaction of animals to experimentally induced convulsions after thyroparathyroidectomy.
      i. Camphor or absinth.
      ii. Electrical excitation.
      iii. Occlusion of the head arteries.
  B. Changes in the concentration of calcium and phosphorus.
    1. In control animals, or in other animals with lesions not involving the thyroparathyroids.
      (a) Pure controls.
        i. Camphor or absinth.
        ii. Electrical excitation.
        iii. Occlusion of the head arteries.
      (b) Plus curare.
        i. Camphor or absinth.
        ii. Electrical excitation.
        iii. Occlusion of the head arteries.
      (c) Plus bromides.
        i. Camphor or absinth.
      (d) Motor area ablation.
        i. Camphor or absinth.
      (e) Transection of the spinal cord.
        i. Camphor or absinth.
    2. In animals after thyroparathyroidectomy.
      (a) Uncomplicated.
        i. Camphor or absinth.
        ii. Electrical excitation.
        iii. Occlusion of the head arteries.
      (b) Plus previous bromide feeding.
        i. Camphor or absinth.
      (c) Plus curare.
        i. Camphor or absinth.
        ii. Electrical excitation.
  C. Changes in the concentration of blood sugar after thyroparathyroidectomy.
  D. Comparison with effects of adrenalectomy.
IV. Discussion.
V. Summary.

I. GENERAL STATEMENT.

A. The General Phenomena of a Convulsion.

The general phenomena of convulsions of experimental or pathological origin, the latter being restricted to what we may term general epilepsy, have been presented in other papers, so that we give here only a brief statement, merely for convenience of treatment, rather than for the purpose of attempting to establish hard and fast lines of demarcation. We may group these general phenomena under the following heads.

1. *The Manifestations in the Skeletal Muscles.*—These are clonic or tonic in nature depending upon the pathogenesis—its nature, site of action—and may be general, as the clonic movements in general epilepsy, or more sharply localized in certain groups of muscles, with a definite order of march, as in Jacksonian epilepsy. Further comment is unnecessary here.

2. *Psychic Equivalents.*—This includes a group of manifestations noted clinically but which we have made no previous or present attempt to analyse experimentally. There is much of obscurity, even mystery, in the terminology employed in their description.

3. *Cardiovascular.*—There is, in general, a change in the blood pressure and the pulse rate during a convulsion of experimental origin or in the convulsions of general epilepsy. Experimentally, the cardiovascular change appears after the onset of the convulsion, if this be elicited either by the injection of some toxic agent, such as absinth or camphor, or by electrical excitation of the cerebral cortex. When occlusion of the head arteries is done, the failure of the cerebral circulation occurs first, after which we have the rise of blood pressure and the changes of heart rate. These cardiovascular changes may be extremely variable in convulsions induced by absinth or camphor, presenting all the possible combinations of (a) rise of both blood pressure and pulse rate, (b) fall of blood pressure with rise of heart rate, (c) fall of both blood pressure and heart rate and (d) rise of blood pressure with fall of heart rate. Clinically, rise of both blood pressure and heart rate and fall of blood pressure with rise of heart rate have been observed in general epilepsy.

4. *Visceral.*—Including all the changes which may be due to central excitation of the autonomic system, except those responsible

for the cardiovascular changes, we have (a) pilomotor activity, as shown by the bushing of the tail and erection of hairs on the back of the animal; (b) activity of the skin glands as shown by the drops of moisture accumulating on the pads of the feet; (c) frequent and marked dilation of the stomach; (d) frequent dilation of the colon; (e) general failure of dilation of the small intestine, althought this may sometimes occur in the absence of the changes grouped under (c) and (d); (f) micturition; (g) pupillary dilation with the pupil rigid to light during the convulsion, or sometimes hippus; (h) narrowing of the pupil in Horner's syndrome, or after experimental section of the cervical sympathetic nerves; (i) occasional defecation; (j) increased activity of the salivary glands, and probably other glandular and visceral changes on which there are no good observations as yet.

5. *Chemical.*—The inorganic elements—sodium, potassium, calcium, magnesium, phosphorus, chlorine and others—are necessary elements for the growth and maintenance of the physiological activity of organisms. Experimental determinations of the relative concentrations of many of these elements necessary for plant growth have been carried out in great detail by botanists who have applied the method of Gibbs' phase rule triangle for the more accurate and comprehensive study of the effects of variations of more than two constituents. It has been known for some years that certain inorganic salts necessary for plant growth may be replaced by others. A part of the calcium in a nutrient solution for plants may be replaced by strontium (Jost, Pflanzenphysiologie). Animal physiologists have worked out the theory of balanced solutions from experiments on the activity of surviving tissues such as heart or muscle, and Ringer's or Locke's solutions were familiar to physiologists 30 or 40 years ago. Since that time, we have seen the development of the theory of buffer action in solutions of inorganic salts containing some carbon dioxide, and the rôle of the inorganic bases in the maintenance of acid-base equilibrium has assumed great importance in present day biochemistry and physiology.

Much has been written on the chemical changes taking place in epilepsy, but probably less is known. There have been many analyses of calcium in the blood of epileptics as well as of patients suffering from other types of convulsions, *e. g.*, eclampsia. We have

also Osnato's studies on lactic acid. Less, however, has been done on this phase of the subject experimentally than on some of the others, and one is often left in doubt as to which precedes the other—the chemical change, if any, or the convulsion. We wish, in this paper, to record the changes in the concentration of inorganic calcium and phosphorus in the blood serum before, during and after, convulsions of experimental origin in (a) control animals with or without experimental lesions of the central nervous system and with or without previous administration of bromides as compared to, (b) the changes in the concentration of these same two elements in cats after thyroparathyroidectomy with or without previous administration of bromides, but without experimental lesions of the nervous system.

B. The Various Hypotheses on the Origin of Convulsions.

The more detailed discussions concerning the various hypotheses of the pathogenesis of epilepsy as observed clinically, have been presented in previous papers. They are:

1. That convulsions are due to some chemical substance of a toxic nature, or of some nature which renders them excitatory to the ganglion cells in the central system.

2. That convulsions as observed clinically, are due to some physical excitation, as by a tumor, a depressed fracture or the occurrence of scar tissue in the central system.

3. That convulsions as observed clinically, owe their genesis to some condition directly traceable to a disturbance of normal circulation of the blood or the normal formation and absorption of the cerebro-spinal fluid.

C. The Means of Inducing Convulsions Experimentally.

These various methods have also been discussed in some detail in previous papers, and will receive only brief mention here. They are:

1. The injection of some toxic substance such as camphor or absinth intravenously, or its administration by stomach tube.

2. The electrical excitation of the cerebral cortex. No further comment is needed here.

3. Occlusion of the head arteries to the brain. Further discussion is needless at this point.

In view of the fact that the same remedial measure, or supposedly remedial measure, or the same drug, may act differently upon animals in which convulsions are induced by these different methods, it has seemed desirable to employ all three of them in the present study to see whether or not there is any detectable difference in the chemical changes brought about by any one method of experimental induction of convulsions, as compared with the changes observed when some other method is used.

D. The Effects of Endocrine and Other Bodily Conditions Upon the Incidence of Convulsions.

The endocrine system has received considerable comment from the clinical side in recent years in the attempt to prove or disprove a relationship between such endocrine conditions, real or supposed, and the incidence of epileptic seizures. The literature on this subject has been summarized by Lennox and Cobb and by Krause and Schum. Experimentally, it has been shown that the intravenous injection of adrenalin reduces the minimal convulsive dose and lethal dose of absinth. The injection of caffeine before or simultaneously with, adrenalin, may reduce the lethal dose still more. The minimal convulsive dose, lethal dose and the total dosage per pound of absinth are reduced by adrenalectomy. It has been shown also, that thyroidectomy decreases the minimal convulsive dose of absinth, although it has not been shown so clearly that the injection of thyroxin has any effect upon convulsions arising from the injection of drugs. One object of this paper is to present some further experimental evidence upon the effect of thyroparathyroidectomy upon the genesis of the general phenomena of the convulsion, together with a little additional information upon the effects of adrenalectomy, particularly as regards some of the chemical changes occurring during convulsions of experimental origin.

II. EXPERIMENTAL TECHNIQUE AND PROCEDURE.

A. Removal of the Thyroparathyroid Combination.

We chose the thyroparathyroid combination because of the known relationship to changes in the concentration of calcium and phosphorus in the blood (Greenwald, 1924, 1931). The thyroids and parathyroids were removed aseptically at one operation, and

the calcium and phosphorus determined. The animals were kept scrupulously clean in special cages. Only two infections of the neck occurred during the entire series and these were discarded for experimental purposes. Forty-eight hours, or less, after the operation, tetany was usually clearly demonstrable. The animals were kept in a uniform temperature—about 70 degrees, and most of the work was carried on in the spring and early summer when cats are usually in the best physical condition. The duration of life in about 80 per cent of thyroparathyroidectomized cats under optimal conditions, without remedial measures, is from four to six days, provided the glands have been completely removed at one operation.

The animals fell into two series:

I. Those in which thyroparathyroidectomy was done without any other procedure than the choice of diet.

II. Those animals which had received one gram of sodium bromide daily in a mixed diet for from 10 to 14 days previous to the removal of the thyroparathyroids. In these cats, after the operation, the dosage of bromide was cut down to one-half, or one-quarter of a gram daily, instead of a gram. Previous to operation the animals showed motor incoordination as a result of the bromide. They would fall over easily and the hind legs were weak so that the animals had difficulty in walking. The gait was unsteady and reeling. In the earlier stages of bromide feeding, some excitement appeared before motor incoordination developed. At the end of two weeks, however, such excitement had disappeared and the animals were quiet and sleepy. Previous observations (Notkin and Pike) had shown satellitosis and even neuronophagia as the result of the administration of large doses—one gram—of sodium bromide daily.

Following thyroparathyroidectomy, these animals became much brighter and more alert, and motor incoordination was diminished within five or six hours. In control cats, motor incoordination persists for several days after the cessation of bromides. Those cats in which the thyroparathyroids were removed during the stage of excitement from bromides were quiet as soon as they had recovered from the effects of the anæsthetic, and remained so. These animals lived under ordinary laboratory conditions for from 14 to 28 days without the usual development of tetany. The characteristic differences in general appearance and deportment of cats after thyroparathyroidectomy, with and without previous ad-

ministration of bromide are shown in Fig. 1. The gray striped cat on the right has not received any bromides, while the yellow and white striped cat on the left had received one gram of sodium bromide daily for 10 days previous to operation. Both animals were operated on upon the same day, within an hour of each other, and the photograph was taken 48 hours later. Some animals of this group survived as long as 30 days without any appearance of tetany. Before that time, however, symptoms of thyroid deficiency had become manifest.

B. The Technique of Experimental Elicitation of Convulsions.

The experimental procedure followed in the elicitation of convulsions by drugs has been described in detail elsewhere (Pike, *et al.*, 1929). The animal was tied out upon an operating table and two to three cubic centimeters of a 1 per cent solution of novocaine were injected into Scarpa's triangle. When this had become effective, the femoral vein was exposed and the animal was ready for the intravenous injection of the standard solution of camphor monobromide (10 grams to 100 cc. of 95 per cent alcohol) or of absinth (1 cc. of oil of absinth to 19 cc. of 95 per cent alcohol). If the cortical motor area was to be exposed, the cat was etherized and the skull trephined in the frontal region. Thereafter ether was intermitted and the electrical excitation could be begun 20 to 30 minutes later. The procedure followed in the elicitation of convulsions by occlusions of the head arteries has also been described elsewhere (Stewart, *et al.*, 1906).

III. EXPERIMENTAL RESULTS.

A. The General Reaction of Animals to the Different Methods of Eliciting Convulsions.

Before one can say what is the effect of thyroparathyroidectomy, with or without previous or subsequent administration of bromides, upon the reaction of an animal to any of the different methods of eliciting convulsions experimentally, it is necessary to have some standard of comparison by which the effects may be judged. This basis of comparison is afforded in part by some previous experiments and in part by new experiments upon control animals with

FIG. 1.—Shows the appearance of two animals 48 hours after thyroparathyroidectomy. The gray and white cat at the left had received one gram of sodium bromide daily before operation. The striped cat at the right had received no bromides.

and without previous administration of bromides. Since it is not feasible to base any conclusions of the effects of thyroparathyroidectomy upon the reaction of the animals to electrical excitation of the cerebral cortex by comparing these effects with those obtained upon control animals by the administration of absinth or camphor, it seems desirable to summarize separately the effects of each of the three different methods of eliciting convulsions in control animals.

TABLE I.

THE EFFECT OF CAMPHOR MONOBROMIDE ON CONTROL CATS.

Weight in pounds.	Minimal convulsive dose per lb., cc.	Total dose (minimal), cc.	Number of convulsions.	Lethal dose per lb., cc.	Total dosage camphor, cc.	Total dosage per lb., cc.
6.0	0.025	0.15	5	0.040	1.25	0.21
7.5	0.028	0.21	8	0.056	1.35	0.19
7.5	0.033	0.25	9	0.043	1.20	0.16
6.5	0.028	0.18	9	0.040	.89	0.13
6.0	0.023	0.14	10	0.030	.86	0.14
8.25	0.019	0.16	6	0.034	.88	0.10
7.0	0.021	0.15	11	0.039	1.16	0.16
7.5	0.015	0.11	7	0.040	1.33	0.18
8.0	0.025	0.20	8	0.040	1.50	0.27
8.25	0.021	0.17	6	0.044	2.25	0.20
8.0	0.022	0.18	4	0.040	1.60	0.22
5.0	0.024	0.12	8	0.042	1.10	0.18
6.0	0.023	0.14	9	0.039	1.10	0.20
6.6	0.022	0.15	7	0.041	1.23	0.21
9.0	0.022	0.20	11	0.038	1.90	0.21
Average	0.020		8	0.040		0.18

I. THE EFFECT OF CONVULSANT DRUGS.

i. We have presented in an earlier paper the reaction of animals with and without previous administration of bromides to the intravenous injection of absinth (Pike, Notkin, Coombs, Weingrow). In general, the minimal convulsive dose of absinth is raised slightly by previous administration of bromides, but the number of successive convulsions which the animal will withstand, as well as the lethal dose, is generally reduced.

Since camphor was the convulsant drug, we give the following tabular summary of results of 15 control cats. (Table I.)

Concerning the effect of previous administration of bromides upon the reaction of animals to intravenous injection of camphor, we give the following table of results obtained from seven cats. (Table II.)

ii. Electrical excitation of the cerebral cortex. Previous experience has shown that control animals will withstand from 35 to 55 successive excitations of the cerebral cortex before death. After previous administration of bromides, this number may rise to 80 or more.

iii. Occlusion of the head arteries. Previous experience has shown that ordinarily vigorous animals will withstand from 9 to 18 succesive short temporary occlusions of the head arteries before succumbing. Or, in terms of minutes of total anæmia due to successive short occlusions, from 25 to 35 minutes. Both the number of consecutive occlusions and the total duration of the periods of anæmia are reduced by previous administration of bromides.

TABLE II.

THE EFFECT OF CONVULSANT DRUGS ON CONTROL CATS TREATED WITH BROMIDES.

Weight in pounds.	Minimal convulsive dose per lb., cc.	Total dose (minimal), cc.	Number of convulsions.	Lethal dose per lb., cc.	Total dosage camphor, cc.	Total dosage per lb., cc.
7.0	0.029	0.20	1	0.032	0.70	0.103
6.75	0.024	0.16	2	0.028	0.64	0.095
5.5	0.030	0.16	1	0.033	0.55	0.106
7.25	0.033	0.24	1	0.035	0.80	0.110
8.0	0.031	0.25	0	0.031	0.80	0.105
6.5	0.026	0.17	1	0.029	0.65	0.100
7.5	0.028	0.21	2	0.031	0.75	0.102
Average	0.029		1	0.031		0.103

2. THE REACTION OF ANIMALS TO EXPERIMENTALLY INDUCED CONVULSIONS AFTER THYROPARATHYROIDECTOMY.

i. Convulsant Drugs (Camphor Monobromide).

(a) Statistical versus direct methods of comparison. In view of the range of the minimal convulsive dose of camphor or absinth in control animals, there is some danger in drawing conclusions as to the effect of any given experimental procedure upon the mini-

mal convulsive dose, by a purely statistical comparison with the results obtained upon control animals. The more certain method is to determine the minimal convulsive dose in an animal before any further experimental procedure is attempted. This method, however, has not always been feasible in our experiments and we have applied the method of statistical comparison. We have not, for example, determined the minimal convulsive dose of camphor or absinth in animals before beginning bromide therapy with sub-

TABLE III.

THE EFFECT OF CONVULSANT DRUGS ON CATS AFTER THYROPARATHYROIDECTOMY.

Weight in pounds.	Minimal convulsive dose per lb.	Total dose (minimal).	Number of convulsions.	Lethal dose per lb.	Total dosage camphor.	Total dosage per lb.
9.0	0.012	0.11	10	0.030	0.87	0.096
8.0	0.009	0.07	3	0.010	0.21	0.026
8.0	0.01	0.08	6	0.022	0.53	0.066
8.0	0.01	0.08	4	0.014	0.19	0.024
6.0	0.008	0.05	4	0.011	0.12	0.020
5.5	0.009	0.05	3	0.015	0.21	0.038
4.9	0.01	0.05	3	0.014	0.12	0.025
7.0	0.01	0.07	4	0.010	0.07	0.010
7.5	0.009	0.07	6	0.026	0.53	0.071
6.0	0.01	0.06	7	0.013	0.15	0.021
5.5	0.012	0.07	3	0.016	0.28	0.050
8.5	0.01	0.09	4	0.016	0.33	0.038
6.5	0.012	0.08	8	0.014	0.25	0.023
6.4	0.01	0.07	4	0.018	0.28	0.043
Average	0.010		5	0.016		0.038

sequent removal of the thyroparathyroids, but have administered absinth only after thyroparathyroidectomy. Some of the results have been so constant and so striking under these conditions as compared to their absence, so far as our observations go, in any control animals, or to their reduced magnitude in control animals, as to constitute a reasonably valid statistical proof.

The minimal convulsive dose, the number of successive convulsions, the lethal dose and the total dosage per pound are all reduced, as compared to controls, after thyroparathyroidectomy without previous administration of bromides. (Table III.)

(b) After previous administration of bromides, the minimal convulsive dose, lethal dose and total dosage per pound are greater than

when bromides are not given. (Table IV.) We would say that, compared with the action of bromides upon control cats, the convulsant effects of camphor after bromides are greater after thyroparathyroidectomy. That is, the bromides seem to have somewhat less effect upon these animals than upon controls. The absence of the post bromide restlessness after thyroparathyroidectomy has already received notice.

ii. Electrical Excitation of the Cortex.

(a) Without previous administration of bromides. When convulsions are induced by electrical excitation of the cortical motor area in cats from which the thyroparathyroids have been removed, the number of excitations which can be done ranges between 8 and 18 as against 35 to 55 in control cats. The convulsions, although fewer in number, are usually more intense and of longer duration than in controls, often persisting from 45 to 100 seconds after excitation with the tetanizing current is over. So far as may be judged, the intensity of the excitation required to elicit the convulsion is less than in controls, the secondary coil of the inductorium being farther out from the primary, other factors apparently remaining the same. But, since we have no measure of the amount of work necessary to elicit a convulsion under any conditions, we cannot say that less work is necessary to elicit a convulsion in cats after thyroparathyroidectomy than in controls. There was usually an early onset of the tonic element of the convulsion, which, in controls, does not appear until late in the experiment. In this series, the limbs often became rigid in tonic extension, with a temporary cessation of respiration, following a few clonic movements, as early as the fourth or fifth excitation of the cortical motor area. With each successive excitation, the clonic element diminished, and the tonic element increased until, after four or five more excitations, the animal succumbed. If, at the period when tonic extension only was present, calcium gluconate was injected intravenously, further excitation of the cortex brought about a return of clonic convulsions and the number which could be elicited was considerably increased.

(b) After previous administration of bromides, animals with the thyroparathyroids removed will withstand a considerably

TABLE IV.

THE EFFECT OF CONVULSANT DRUGS ON THYROPARATHYROIDECTOMIZED CATS, PREVIOUSLY TREATED WITH BROMIDES.

Weight in pounds.	Minimal convulsive dose per lb., cc.	Total dose (minimal), cc.	Number of convulsions.	Lethal dose per lb., cc.	Total dosage camphor, cc.	Total dosage per lb., cc.
7.0	0.026	0.18	1	0.034	1.03	0.148
7.5	0.029	0.22	2	0.033	1.16	0.155
6.75	0.030	0.20	0	0.030	1.06	0.150
9.0	0.028	0.25	1	0.031	1.31	0.141
8.2	0.032	0.26	2	0.035	1.19	0.145
6.5	0.035	0.22	0	0.035	1.04	0.160
Average	0.030		1	0.033		0.149

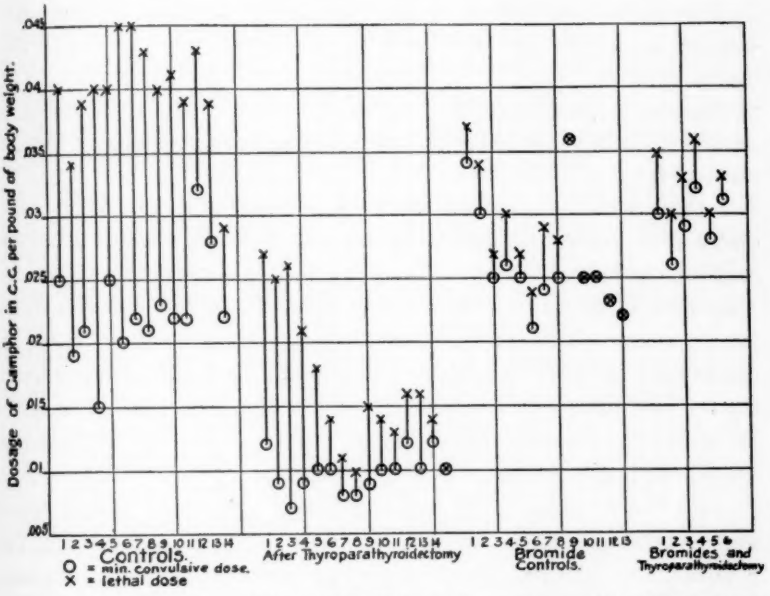

FIG. 2.—The minimal convulsive and lethal doses of camphor monobromide per pound (a) in control animals, (b) after thyroparathroidectomy, (c) controls previously fed on bromides, and (d) animals fed bromides before thyroparathyroidectomy. The dosage of camphor is given on the vertical line at the left (in hundredths of a centimeter per pound). The arabic numerals below the horizontal line indicate the number of animals in each group. The open circles represent the minimal convulsive dose, and the crosses the lethal dose.

greater number of cortical excitations than cats not so treated, although the actual convulsions thus produced are very slight. The number of excitations which may be done before the death of animals in this series has been found to range between 20 and 32.

iii. Occlusion of the Head Arteries.

After thyroparathyroidectomy, the number of brief repeated occlusions of the head arteries which can be done before death is less than in controls. From four to eight occlusions are the usual number of anæmic responses which can be elicited, and the total occlusion time is cut down to between 8 and 15 minutes. The character of the single response to occlusion, however, appears unchanged from that in the controls. Occlusion of the head arteries has not been done in animals which received bromides prior to the removal of the thyroparathyroids.

The general summary of the reaction of animals to convulsive agents after thyroparathyroidectomy brings out the following facts:

Although the onset of the convulsion after injection of the drug is more likely to be delayed after thyroparathyroidectomy than in controls:

(1) The minimal convulsive dose, the lethal dose and the total dosage of the convulsant drug are significantly lower. The convulsions are of the clonic type. Four or five successive convulsions may follow the injection of a single dose which, in a control, would be subminimal. More than two successive convulsions from the same dose are rare in control animals until a dosage large enough to be just sublethal is reached. The actual duration of a single convulsion is usually greater than in control animals and generalized twitches persist longer.

(2) The number of excitations of the cortical motor area which can be done before the animal succumbs is greatly diminished. The character of the convulsions, moreover changes from clonic to tonic at an early period in the experiment.

(3) The number of occlusions of the head arteries which can be done, as well as the total occlusion time, is markedly diminished. There is little or no change in the character of the individual response.

B. Changes in the Concentration of Calcium and Phosphorus.

Samples of blood were taken at the beginning of each experiment and again after a number of convulsions varying from two or three to six or seven with the convulsant drug, from 10 to 25 in the case of electrical excitation of the cortex, and from two to six in occlusion of the head arteries. The calcium was determined by the Clark-Collip modification of the Kramer-Tisdale method (Kramer, 1925), and the phosphorus by the method of Youngberg (1930).

I. VARIATIONS IN CALCIUM AND PHOSPHORUS IN CONTROL ANIMALS.

(a) Animals in which there is no other experimental procedure. Samples of blood were taken—8 to 10 cubic centimeters—before any injection of a convulsant drug or any electrical excitation of the cerebral cortex was done. Ten cubic centimeters of a 0.9 per cent solution of sodium chloride was injected intravenously after the withdrawal of this first sample of blood. We can say that in control experiments the withdrawal of this amount of blood and its replacement by saline solution does not change the minimal convulsive dose of the drug appreciably. A series of convulsions was then induced; either by drugs, by electrical excitation of the cortex, or by occlusion of the arteries to the head. When the animal showed signs of approaching death, as judged by our observations on other animals during earlier experiments, a second sample of 8 to 10 cc. of blood was taken. The concentration of ionized calcium and inorganic phosphorus in the blood serum is given in Table V.

In the control animals before any convulsion was induced, the calcium ranged between 9.0 and 10.7 milligrams per 100 cc. of serum, with an average of 10.0 and an average deviation of plus or minus 0.5 mg.; the inorganic phosphorus ranged between 4.8 and 6.4 milligrams per 100 cc. of serum, with an average of 5.5 mg., and an average deviation of plus or minus 0.5 mg. After the series of convulsive seizures, the range of the calcium was between 10.0 and 14.9 mg., with an average of 12.0 mg., and an average deviation of plus or minus 1.3 mg.; the phosphorus was between 5.6 and 9.6 mg., with an average of 7.5 and an average deviation of plus or minus 1.1. In both the drug-induced convulsions, and those

elicited by electrical excitation of the cortex, all animals showed some increase in both calcium and phosphorus; in the case of occlusion of the head arteries about half the animals showed an increase in the calcium and phosphorus, the remainder not being altered. The magnitude of the change was about the same, whatever the agent by which the convulsions were induced. (Table VI.) At post-mortem, the stomach and large intestine were found to be dilated, the bladder was empty and the lungs showed numerous petechial hemorrhages in practically all cases.

TABLE V.

CALCIUM AND PHOSPHORUS BEFORE AND AFTER EXPERIMENTAL CONVULSIONS, IN CONTROLS.

Number of convulsions.	How elicited.	Calcium—mg./100 cc. serum.				Ca/P ratio before convulsions.	Phosphorus—mg./100 cc. serum.				Ca/P ratio after convulsions.
		Before convulsions.	After convulsions.	Change mg.	Change %		Before convulsions.	After convulsions.	Change mg.	Change %	
11	Drugs....	9.5	10.1	+0.6	6%	1.9	4.9	5.6	+0.7	14%	1.8
8	Drugs....	9.6	14.9	+5.3	55%	1.5	6.4	9.6	+3.2	50%	1.5
6	Drugs....	9.0	12.3	+3.4	38%	1.8	4.8	7.1	+2.3	48%	1.7
7	Drugs....	10.7	11.4	+0.7	6%	2.2	4.8	7.0	+2.3	45%	1.6
10	Drugs....	10.6	11.5	+0.9	9%	1.7	6.2	9.0	+2.8	45%	1.3
27	Electrical.	9.5	12.9	+3.4	35%	1.6	5.8	8.8	+3.0	51%	1.4
30	Electrical.	10.4	13.2	+2.8	27%	1.7	6.0	7.2	+1.2	20%	1.8
25	Electrical.	10.4	11.9	+1.5	14%	1.7	6.1	7.7	+1.6	26%	1.5
18	Electrical.	9.4	10.0	+0.6	6%	1.8	5.0	5.6	+0.6	12%	1.8
Average.....		10.0	12.0	+2.0	+20%	1.8	5.5	7.5	+2.0	+36%	1.6
Average deviation		±0.5	±1.3	±1.4	..	...	±0.5	±1.1	±0.8	..	...

(b) In the second group of controls, curare was administered about 15 minutes before the first injection of the convulsant drug or electrical excitation of the cortex. There was no further activity in any case. The blood pressure response after each cortical excitation or injection of the drug was the only evidence of its potency. There was no increase either in calcium or phosphorus in any animal. In each case, there was a slight fall either in the calcium or the phosphorus or both. (Table VII.) Post-mortem examination showed flabby stomach and intestines and frequently a bladder filled with urine. This is in line with the observation of

TABLE VI.

CALCIUM AND PHOSPHORUS IN THE BLOOD SERUM OF CEREBRAL ANÆMIA CONTROLS.

Number of occlusions.	Calcium—mg. per 100 cc. serum. Before.	After.	Ca/P ratio before.	Phosphorus—mg. per 100 cc. serum. Before.	After.	Ca/P ratio after.
2	10.2	10.5	2.2	4.5	4.7	2.2
3	10.0	11.8	2.9	3.4	4.5	2.6
3	9.8	10.3	1.5	6.2	8.3	1.2
4 (young)	10.1	9.4	2.2	4.5	4.6	2.0
4	9.6	10.8	2.0	4.7	3.7	2.8
5	10.1	11.4	2.4	4.2	4.6	2.4
5	9.2	10.3	2.0	4.6	4.5	2.2
6	11.7	13.8	2.4	4.8	5.0	2.4
6	9.4	9.3	1.4	6.7	6.5	1.4
6	10.0	8.8	2.0	5.0	7.0	1.2
6	11.1	10.1	3.4	3.2	4.8	2.1
7	10.2	10.6	2.8	4.2	4.2	2.5
8	10.5	12.1	2.0	5.1	5.5	2.3
9 (preg)	8.9	10.7	2.2	4.0	4.5	2.3
9	10.2	10.8	1.7	5.8	6.3	1.7
10	10.1	10.5	2.8	3.5	5.7	1.9
11	10.1	12.3	1.5	6.5	6.3	1.9
11	9.6	10.2	1.5	6.0	5.8	1.7
11	10.1	10.1	1.8	5.4	4.8	2.1
12	10.0	10.8	2.2	4.5	4.5	2.4
Average	10.0	10.1	2.0	4.8	5.3	1.9
	CONTROLS PLUS CURARE.					
6	11.6	11.7	2.5	4.5	7.9	1.5
4	11.1	11.2	1.5	7.1	7.2	1.5

TABLE VII.

CALCIUM AND PHOSPHORUS BEFORE AND AFTER CONVULSANTS, IN CONTROLS UNDER CURARE.

Calcium—mg. per 100 cc. serum. Before.	After.	Change.	Phosphorus—mg. per 100 cc. serum. Before.	After.	Change.
9.9	9.8	..	5.1	4.0	— 1.1
10.0	8.7	— 1.3	5.5	5.0	— 0.5
10.2	9.0	— 1.2	5.4	4.7	— 0.7

Edmunds and Roth, that under curare, the bladder muscle of the cat contracts and then relaxes, after which the stimulant action of small doses of physostigmine is prevented, showing that the paralysis affects some structure between the central system and the ending.

(c) In the third group of control animals, one gram of sodium bromide had been administered daily in the food for about two weeks prior to the elicitation of the convulsions. Under these conditions, as previously shown, few, if any, general clonic convulsions can be elicited by the convulsant drugs. In nine animals of this series, the average concentration of calcium before the administration of the convulsant was 10.5 milligrams per 100 cc. of serum, with an average deviation of plus or minus 0.4 mg., and at the conclusion of the experiment, 9.8 mg. per 100 cc. of serum, with an average deviation of plus or minus 0.4 mg. The average concentration of phosphorus at the beginning of the experiment was 5.3 mg. per 100 cc. serum, with an average deviation of plus or minus 0.5 mg., and at the end, 5.0 mg. with an average deviation of plus or minus 0.5 mg. (Table VIII.) From these figures, it may

TABLE VIII.

CALCIUM AND PHOSPHORUS IN CONTROLS TO WHICH BROMIDE HAS BEEN ADMINISTERED FOR TEN TO FOURTEEN DAYS.

Calcium—mg./100 cc. serum.				Ca/P ratio before convulsions.	Phosphorus—mg./100 cc. serum.				Ca/P ratio after convulsions.
Before convulsions.	After convulsions.	Change mg.	Change %		Before convulsions.	After convulsions.	Change mg.	Change %	
10.6	9.3	−1.3	−12%	1.6	6.5	5.0	−1.5	−30%	1.8
11.0	10.2	−0.8	− 8%	1.8	6.0	6.2	none		1.6
10.3	9.5	−0.8	− 8%	1.6	6.1	5.7	−0.4	−10%	1.6
10.7	10.2	−0.5	− 5%	2.0	5.0	4.5	−0.5	−11%	2.2
11.1	10.6	−0.5	− 5%	2.2	5.0	5.0	none		2.0
10.1	9.6	−0.5	− 5%	1.8	5.4	4.5	−0.5	−11%	2.1
9.9	9.6	−0.3	− 3%	2.0	4.8	4.3	−0.5	−10%	2.2
10.9	10.1	−0.8	− 9%	2.4	4.5	4.5	none		2.2
10.2	9.5	−0.7	− 7%	2.1	4.8	4.4	−0.4	− 8%	2.2
Average... −10.5	9.8	−0.7	− 7%	2.0	5.3	5.0	−0.3	− 5%	2.0
Average deviation. ±0.4	±0.4	±0.2	..	...	±0.5	±0.5	±0.1	..	...

be seen that the concentration of calcium and phosphorus in the blood of cats which have undergone bromide medication is practically identical with the averages for untreated controls. But there is a wide divergence after convulsions have been elicited.

	Before convulsions.		After convulsions.	
	Ca—mg./100 cc.	P—mg./100 cc.	Ca.	P.
Average of controls.....	10.0	5.5	12.0	7.5
Average after bromides.....	10.5	5.3	9.8	5.0

(d) In the fourth group of controls, the cortical motor areas were removed about two hours before the animals were used for experiment. Samples of blood were taken and the convulsant drug was administered in the usual manner. Few clonic movements appeared, the response being chiefly that of tonic extension—the usual result after acute removal of the cortical motor areas. Samples of blood were again taken toward the close of the experiment, and the calcium and phosphorus determined. Table IX shows that the increase in calcium and phosphorus is considerably less than in controls in which clonic, as well as tonic, convulsions occurred. The average concentration of calcium in milligrams per 100 cc. of serum was 9.8 and the phosphorus 6.1. Following convulsions, the calcium rose to 10.7 and the phosphorus to 7.3. Post-mortem examination showed less marked dilation of the stomach; sometimes the dilation was wholly absent. The bladder was usually empty. There were few, if any, petechial hemorrhages in the lungs.

TABLE IX.

CALCIUM AND PHOSPHORUS IN CONTROLS AFTER REMOVAL OF MOTOR AREAS.

	Calcium—mg./100 cc. serum.				Ca/P ratio before convulsions.	Phosphorus—mg./100 cc. serum.				Ca/P ratio after convulsions.
	Before convulsions.	After convulsions.	Change mg.	Change %		Before convulsions.	After convulsions.	Change mg.	Change %	
	9.5	10.7	+1.2	+12%	1.4	6.5	7.1	+0.6	+ 9%	1.5
	10.5	10.2	−0.3	..	1.7	6.0	6.4	+0.4	+ 6%	1.6
	8.8	10.0	+1.2	+13%	1.4	6.0	8.0	+2.0	+33%	1.2
	10.2	11.8	+1.6	+15%	1.6	6.1	7.7	+1.6	+26%	1.5
Average....	9.8	10.9	+1.1	+11%	1.6	6.1	7.3	+1.2	+20%	1.5

In two animals, the spinal cord was transected in the upper thoracic region 24 hours before the administration of the convulsant drug. The calcium and phosphorus figures are as follows:

	Before convulsions.		After convulsions.	
	Ca.	P.	Ca.	P.
Cat number 1.....	10.0	5.5	10.9	4.0
Cat number 2.....	10.1	4.3	10.0	4.5

2. VARIATIONS IN CALCIUM AND PHOSPHORUS IN ANIMALS AFTER THYROPARATHYROIDECTOMY.

(a) In the first group, there were no other experimental procedures intervening between the removal of the thyroparathyroids

TABLE X.

CALCIUM AND PHOSPHORUS BEFORE AND AFTER EXPERIMENTAL CONVULSIONS AFTER THYROPARATHYROIDECTOMY.

Number of convulsions.	How elicited.	Calcium—mg./100 cc. serum.				Ca/P ratio before convulsions.	Phosphorus—mg./100 cc. serum.				Ca/P ratio after convulsions.
		Before convulsions.	After convulsions.	Change mg.	Change %		Before convulsions.	After convulsions.	Change mg.	Change %	
10	Drugs....	5.2	6.8	+1.6	+30%	1.1	4.6	10.6	+6.6	+143%	0.6
7	Drugs....	5.3	7.2	+1.9	+36%	1.0	5.3	8.3	+3.0	+ 56%	0.8
6	Drugs....	6.6	8.5	+1.9	+29%	0.9	6.9	8.7	+1.8	+ 26%	0.9
6	Drugs....	5.8	9.2	+3.4	+58%	1.0	5.6	6.0	+0.4	+ 7%	1.5
9	Drugs....	6.0	7.5	+1.5	+25%	1.2	5.0	7.5	+2.5	+ 50%	1.0
12	Drugs....	5.8	6.4	+0.6	+10%	1.0	5.5	7.2	+1.7	+ 31%	0.9
16	Electrical.	5.3	8.5	+3.2	+60%	0.8	6.2	9.9	+3.7	+ 59%	0.8
7	Electrical.	5.7	9.5	+3.8	+66%	0.9	6.0	6.5	+0.5	+ 8%	1.4
12	Electrical.	7.0	10.5	+3.5	+50%	1.2	5.9	8.7	+2.8	+ 47%	1.2
Average.....		5.8	8.2	+2.4	+40%	1.0	5.9	8.2	+2.3	+39%	1.0
Average deviation		±0.4	±1.1	±0.8	..	...	±0.5	±1.7	±1.3	..	...

and the elicitation of the convulsions except in one group, in which the cerebral cortex was exposed under ether anæsthesia half an hour before electrical excitation was begun. The results are given in Table X. It is worthy of note that the administration of ether half an hour before the first sample of blood was drawn did not affect the concentration of calcium or of phosphorus appreciably. The calcium showed the usual 45 to 50 per cent fall after thyro-

parathyroidectomy, while the average concentration of the phosphorus was the same as, or slightly higher than, in controls.

After elicitation of the convulsions by drugs or electrical excitation, there was an increase in both the calcium and phosphorus of the blood serum. There was never any fall in either. The actual increase of calcium in milligrams—an average of 2.4 mg./100 cc. serum—was even slightly greater than the average increase—2.0 mg./100 cc. serum—in the animals of group (a) of the control series, and on a percentage basis was an increase of about 40 per cent as against 20 per cent in the control series.

The average change of phosphorus in milligrams—2.3 mg./100 cc. serum—was much closer to the order of magnitude in the control series. The percentage increase of phosphorus was 39 as compared with 36 for the controls. The ratio of the actual increase of calcium to the increase of phosphorus expressed in milligrams is the same in this group (2.4/2.3) and in group (a) of the controls, (2.0/2.0), or a one to one correspondence in each.

When the head arteries were occluded in cats 48 hours after thyroparathyroidectomy, it has been observed that the number of occlusions and the total occlusion time were much reduced from that of the controls. The concentration of calcium in the blood serum was always higher after the periods of anæmia than before. The phosphorus however, rose, fell, or remained stationary with apparently no ascertainable relationship to the calcium. (Table XI.)

(b) In the group of cats to which sodium bromide had been administered for two weeks, little or no tetany was observed following removal of the thyroparathyroids. The concentration of calcium and phosphorus becomes of special interest here. (Table XII.) The calcium for the group averaged 7.5 mg./100 cc. serum as compared to 5.8 mg./100 cc./serum of cats to which bromides were not administered. The concentration of phosphorus, on the other hand, was low—5.2 mg./100 cc. serum for this group as compared to 5.5 and 5.9 mg./100 cc. of serum for the controls and after thyroparathyroidectomy, respectively—but was practically identical with the average phosphorus (5.3 mg./100 cc. serum) in the controls to which bromide had been administered. The actual increase in calcium in this series of experiments (in which there was very little clonic activity) averaged 1.2 mg./100 cc. serum, or 16 per cent

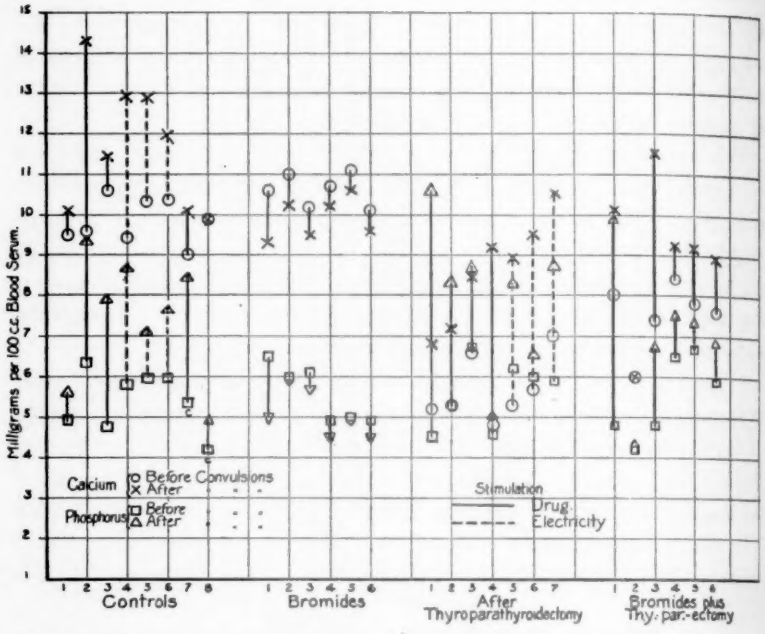

FIG. 3.—The changes in calcium and phosphorus as the result of convulsions in (a) control animals, (b) control animals fed on bromides, (c) animals after thyroparathyroidectomy, and (d) animals fed on bromides before thyroparathyroidectomy. The open circles represent the concentration of calcium before the convulsions were induced and the crosses the concentration of calcium after a series of convulsions. The squares and triangles represent the concentration of phosphorus in milligrams per 100 cc. of blood serum before and after the elicitation of the convulsions. The solid line joining any two symbols indicates that the convulsions were induced by the injection of camphor, and the broken line that electrical excitation of the cortex was employed. The numerals on the vertical axis at the left indicate milligrams per 100 cc. of serum. The arabic numerals below the horizontal line indicate the number of animals in each group.

TABLE XI.

CALCIUM AND PHOSPHORUS OF THE BLOOD SERUM DURING CEREBRAL ANÆMIA FOLLOWING THYROPARATHYROIDECTOMY.

Number of occlusions.	Calcium—mg. per 100 cc. serum. Before.	After.	Ca/P before.	Phosphorus—mg. per 100 cc. serum. Before.	After.	Ca/P after.
1	5.2	7.6	1.5	3.5	5.2	1.4
1 (long)	5.4	6.0	1.0	5.4	4.7	1.2
3	5.3	6.9	0.9	5.5	4.5	1.5
4	4.5	5.1	1.0	4.5	5.5	0.9
4	5.3	6.5	0.9	5.7	5.6	1.1
6	5.1	6.2	1.1	4.4	5.2	1.1
Average	5.1	6.4	1.0	4.8	5.1	1.2
AFTER THYROPARATHYROIDECTOMY PLUS CURARE.						
3	5.3	5.4	1.0	5.4	4.7	1.1
5	5.5	5.2	1.0	5.6	5.1	1.0

TABLE XII.

CALCIUM AND PHOSPHORUS BEFORE AND AFTER EXPERIMENTAL CONVULSIONS FOLLOWING THYROPARATHYROIDECTOMY AFTER BROMIDE FEEDING.

Calcium—mg./100 cc. serum. Before convulsions.	After convulsions.	Change mg.	Change %	Ca/P ratio before convulsions.	Phosphorus—mg./100 cc. serum. Before convulsions.	After convulsions.	Change mg.	Change %	Ca/P ratio after convulsions.
8.0	10.1	+2.1	+26%	1.6	4.8	10.0	+5.2	+108%	1.0
6.0	5.9	...	....	1.4	4.3	4.5	...	....	1.3
7.4	11.5	+4.1	+55%	1.5	4.8	6.7	+1.9	+ 40%	1.7
8.4	9.2	+0.8	+ 9%	1.3	6.5	7.5	+1.0	+ 15%	1.2
7.8	9.2	+1.4	+18%	1.6	4.6	5.8	+1.2	+ 26%	1.6
7.6	8.9	+1.3	+18%	1.4	5.4	6.5	+1.2	+ 22%	1.3
7.5	7.4	...	....	1.5	4.8	5.8	+1.0	+ 20%	1.2
7.4	7.4	...	....	1.2	6.2	6.9	+0.7	+ 11%	1.0
Average.... 7.5	8.7	+1.2	+16%	1.4	5.2	6.7	+1.5	+ 28%	1.3
Average deviation. ±0.4	±1.3	...	..	...	±0.6	±1.0	...	..	...

while the increase in phosphorus averaged 1.5 mg./100 cc. serum, or 28 per cent.

A group of 12 cats in this series were kept on reduced bromide feeding from one to four weeks after thyroparathyroid-

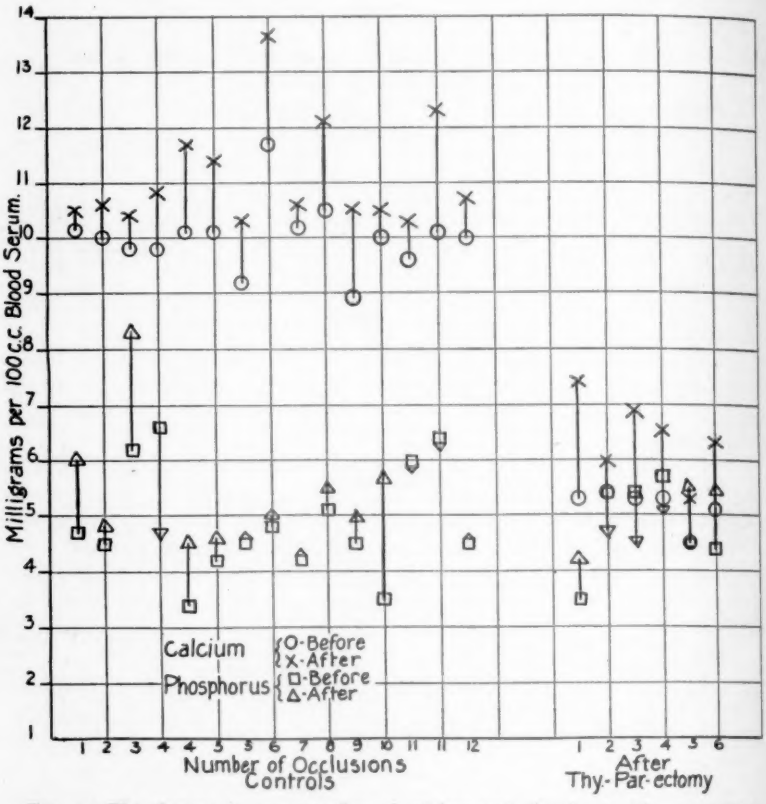

FIG. 4.—The changes in concentration of calcium and phosphorus when convulsions were induced by tying off the arteries to the head in (a) control animals and (b) after thyroparathyroidectomy. The numerals at the left of the vertical axis indicate concentration in milligrams per 100 cc. of serum. The open circles represent the concentration of calcium before, and the crosses the concentration of calcium after, the occlusions of the head arteries. The initial concentration of phosphorus is indicated by the open square, and its final concentration by the triangle. The numerals below the horizontal axis indicate the number of occlusions of the head arteries after which the samples of blood were drawn.

ectomy. None of them showed tetany or other indications of parathyroid insufficiency, although animals which were kept for a period longer than two weeks began to show myxœdema, falling hair and sore eyes typical of thyroid insufficiency. Calcium and phosphorus determinations were made upon these animals at in-

tervals of 2 to 10 days. The curve followed by the calcium and phosphorus during this period presents an interesting contrast to the curve shown by untreated animals after thyroparathyroidectomy. Table XII shows that the calcium never falls as low as in untreated

TABLE XIII.

CALCIUM AND PHOSPHORUS OF BROMIDE-FED CATS AFTER THYROPARATHYROIDECTOMY.

Cat No.	Before operation.	After operation. Days. 1–2	3–4	5–6	7–9	10–12	13–16	17–20	21–24	25–30
1	Ca 10.3	....	Ca 6.4	....	....	....	....	....	...	....
	P 6.2	....	P 5.2	....	....	....	....	....	...	....
2	Ca 10.3	....	Ca 6.6	Ca 6.3	....	Ca 6.6	Ca 8.8	....	...	....
	P 6.1	....	P 5.5	P 4.8	....	P 4.5	P 4.5	....	...	....
3	Ca 10.1	Ca 8.1	....	Ca 8.6	....	Ca 8.8	....	....	...	....
	P 4.3	P 4.3	....	P 4.5	....	P 4.5	....	....	...	....
4	Ca 10.4	Ca 7.7	....	Ca	Ca 8.2	....	Ca 8.4	....	...	....
	P 4.5	P 4.2	....	....	P 5.2	....	P 5.5	....	...	....
5	Ca 10.0	Ca 7.8	....	....	Ca 7.3	....	Ca 7.2	....	...	....
	P 4.0	P 4.3	....	....	P 4.0	....	P 2.0	....	...	....
6	Ca 10.9	Ca 7.9	....	....	....	Ca 8.0	Ca 9.4	....	...	....
	P 4.5	P 5.7	....	....	....	P 6.5	P 4.0	....	...	....
7	Ca 10.3	Ca 7.3	....	Ca 7.5	....	....	....	....	...	....
	P 4.5	P 4.1	....	P 2.5	....	....	....	....	...	....
8	Ca 10.0	....	....	Ca 4.6	....	....	....	....	...	....
	P 4.7	....	....	P 4.0	....	....	....	....	...	....
9	Ca 10.2	....	....	Ca 9.8	....	Ca 9.5	....	....	...	....
	P 4.0	....	....	P 6.0	....	P 6.0	....	....	...	....
10	Ca 10.2	....	....	Ca 6.5	....	....	....	....	...	....
	P 4.8	....	....	P 5.5	....	....	....	....	...	....
11	Ca 10.5	Ca 7.2	....	....	....	....	Ca 7.5	....	...	....
	P 4.9	P 4.4	....	....	....	....	P 4.8	....	...	....
12	Ca 10.4	Ca 7.5	....	....	....	....	....	Ca 7.3	...	Ca 8.5
	P 4.6	P 4.8	....	....	....	....	....	P 5.1	...	P 4.0

cats, and rises to 60 or even 80 per cent of the control values. The phosphorus, however, remains lower than in the controls, and in two cases, fell to a very low level. None of these animals actually died, of thyroparathyroid failure; all were used for one or another type of experiment. We cannot, therefore, say to what limits life

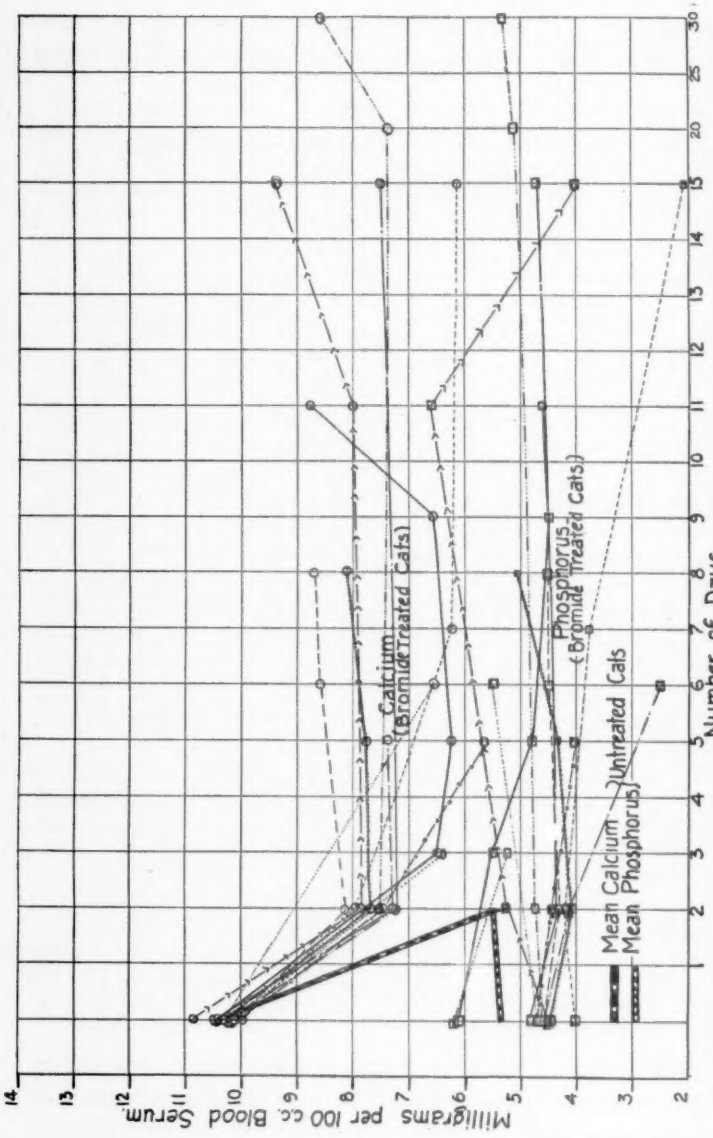

FIG. 5.—A graphic representation of Table XIII. Shows the concentration of calcium and phosphorus day by day in cats previously fed with bromides, after thyroparathyroidectomy. The heavy interrupted black lines at the left show the average concentration of calcium and phosphorus in untreated cats, 48 hours after thyroparathyroidectomy. The vertical line at the left indicates the number of milligrams per 100 cc. of serum. The horizontal line shows the number of days following thyroparathroidectomy.

could be prolonged under bromide medication after removal of the thyroparathyroids, but we can say, that acute failure may be prevented—in cats—by the administration of bromides.

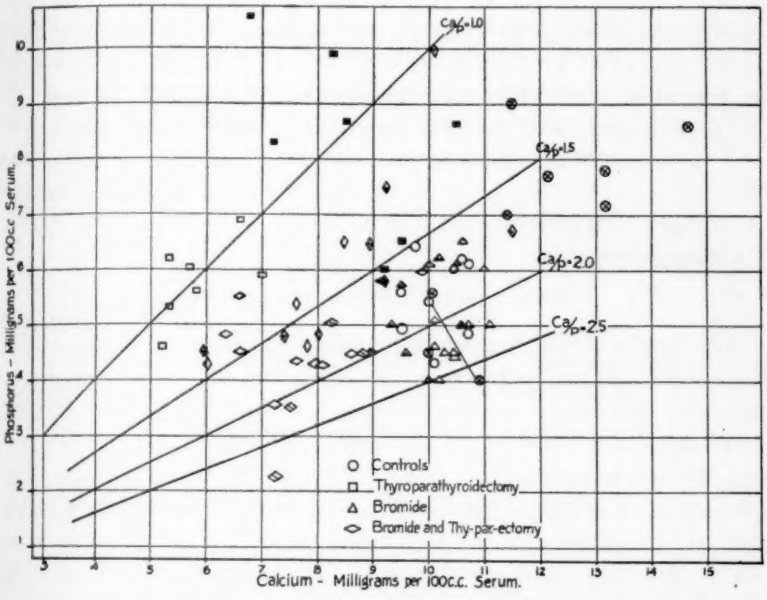

FIG. 6.—A composite graph showing the changes in the concentration of calcium and phosphorus in a series of animals during a series of convulsions. The following groups of animals are represented: (a) controls, circles; in this, as in all other groups, the open figure represents the initial concentration and the figure with the cross lines the concentration after elicitation of convulsions; (b) after thyroparathyroidectomy, the square; (c) controls fed on bromides, triangle; (d) animals which had received sodium bromide previous to thyroparathyroidectomy, the diamond. The concentration of phosphorus in milligrams per 100 cc. of serum is given on the vertical axis to the left, and the concentration of calcium on the horizontal axis. The diagonal lines with the caption Ca/P = 1.0, 1.5, 2.0 and 2.5 respectively indicate the ratio of calcium to phosphorus at all points on each particular line.

(c) When curare was administered to animals of this series the calcium, following the administration of drugs or electrical excitation of the cerebral cortex, varied only within the limits of experimental error. There was a fall in phosphorus in each case, although it was never very great. The animals were able to withstand greater amounts of cortical excitation and greater amounts of drugs than non-curarized animals after thyroparathyroidectomy.

C. Changes in the Concentration of Blood Sugar in Animals After Thyroparathyroidectomy.

UNCOMPLICATED.

For comparison of the deportment of these animals, with that of animals after adrenalectomy, we have estimated the blood sugar before and after convulsions arising from the drug in two animals in which the changes in calcium and phosphorus were typical. In both cases there was an increase in blood sugar from 260 to 500 and from 220 to 290 milligrams respectively. The calcium in these two animals rose from 5.8 to 6.4 and from 6.0 to 7.5 mgms. respectively. The phosphorus rose from 5.5 to 7.2 and from 5.0 to 7.5 respectively.

WITH PREVIOUS BROMIDE FEEDING.

We also measured the changes in the concentration of sugar during convulsions from the drug in two animals to which bromides had been fed for two weeks before thyroparathyroidectomy. Calcium remained practically unchanged in both cases (*i. e.*, 7.5 mg./100 cc. serum to 7.3; and 7.5 to 7.7 mg., respectively). The phosphorus increased from 4.8 to 5.8 and from 6.2 to 6.9 milligrams per 100 cc. serum, and the sugar rose from 190 to 460, and from 170 to 280 milligrams respectively. The concentrations of sugar in the blood under control conditions in these animals, and in those to be mentioned after adrenalectomy, are considerably higher than those ordinarily given. The increase over the values ordinarily given may be due to the method of handling the animals previous to the drawing of the blood. Our object was not so much to get the concentration of sugar under conditions of least possible disturbance, as to get the change in the concentration of sugar which might accompany the other changes in a convulsion or a series of convulsions.

D. Comparison With the Effects of Adrenalectomy.

Changes in the concentration of calcium, phosphorus and blood sugar in experimentally induced convulsions after adrenalectomy.

The similarity of the deportment of animals after adrenalectomy during convulsions of drug origin to that observed after thyroparathyroidectomy raises the question of the possibility of the presence

of certain common factors in the two conditions. In both cases there is a reduction of the minimal convulsive dose, the number of convulsions and the total dosage per pound. We have, therefore, measured the changes in the concentration of calcium, phosphorus and sugar during convulsions induced in animals after (1) uncomplicated adrenalectomy and (2) after adrenalectomy following bromide feeding.

(1) In three cats following removal of the adrenals from 40 to 48 hours earlier, convulsions were induced by camphor. The calcium, phosphorus and sugar were as follows:

	Before convulsions.			After convulsions.		
	Ca.	P.	Glucose.	Ca.	P.	Glucose.
Cat No. 1.....	9.9	5.0	240	10.2	8.2	420
Cat No. 2.....	10.1	6.5	200	...	11.5	360
Cat No. 3.....	11.1	5.2	230	14.5	9.0	535

The figures for an animal which had been treated with bromide for two weeks before adrenalectomy were as follows:

	Before adrenalectomy.	Before convulsions.	After convulsions.
Ca	10.0	..	..
P	4.8	6.0	9.0
Glucose	200	140	125

While the array of figures here is not sufficient to do more than indicate the way for further investigation, the difference in the behavior of the phosphorus is at least interesting. The changes in glucose are in line with what one might expect, especially after treatment with bromides, in which the muscular activity is greatly reduced.

In the untreated cats, there was an average increase of 70 per cent of the inorganic phosphorus after convulsions. In the single animal under bromide medication before adrenalectomy, the increase in phosphorus was 50 per cent. The calcium figures in all cases are within range of the controls, but the calcium phosphorus ratio, which ordinarily remains relatively constant before and after convulsions, undergoes a greater change under these conditions than has been observed elsewhere. In cat No. 1 the ratio changed from 2.0 before, to 1.2 after the convulsions, and in cat No. 3 the change was from 2.1 to 1.6. It would seem that there is a more profound disturbance of the calcium phosphorus balance than after thyroparathyroidectomy. Further investigation of the relation of

the adrenals to phosphorus metabolism from this standpoint would, therefore, be of considerable interest.

SOME GENERAL COMMENTS.

The general treatment of the results may be subdivided under various headings. We may consider first of all, the general phenomena of a convulsion.

The relation of the changes in concentration of calcium, phosphorus and sugar to the pathogenesis of the convulsion. It is apparent that a change which comes on after the convulsion cannot very well have worked backward to induce the convulsion. The changes in concentration of the calcium, phosphorus and sugar must be regarded as a part of the general phenomena of the convulsion; as a result, not as a cause.

The dependence of the change in concentration of calcium and phosphorus upon the degree or amount of muscular activity is shown:

(1) By the fact that no such increases as are observed during or after a typical clonic convulsion occur after the intravenous injection of curare and the consequent paralysis of all the skeletal muscles.

(2) By the fact that any experimental procedure upon the nervous system, such as relatively high transection of the spinal cord or ablation of the cortical motor areas, shortly before the elicitation of the convulsions, which tends to reduce the total amount of muscular work done during a convulsion, tends also to reduce the magnitude of the change in the concentration of the two substances.

The change in concentration of calcium and phosphorus is not a specific effect due to the drug used, since a change of the same magnitude occurs when the cortex is stimulated electrically. The decreased magnitude of the changes as a result of occlusion of the head arteries probably stands in some relation to the decreased amount of actual muscular work during an occlusion of the head arteries as compared to the amount of work following the injection of a drug, or electrical excitation of the head arteries. One should bear in mind that after occlusion of the head arteries cortical activity soon ceases, and during the latter portion of the anæmic response, the cardiovascular change is the most pronounced fea-

ture. The magnitude of the change of the concentration of calcium and phosphorus is apparently more closely related to the activity of the so-called cerebro-spinal nervous system than to the activity of the autonomic—including the sympathetic—system. The results obtained by occlusion of the head arteries agree in this respect with those obtained by camphor or electrical excitation of the cerebral cortex in curarized animals.

It seems fair to conclude therefore, that the changes in the concentration of calcium and phosphorus are related to the activity of the skeletal muscles rather than to any glandular activity evoked by the convulsions, but these results do not, in themselves, show the source of the increased calcium or phosphorus.

Our experimental results are in agreement in so far as the different conditions of experiment will permit comparison, with those of Zagami, Bernardi, and others. Zagami reports a rise in calcium and potassium in the blood serum of dogs after convulsions of experimental origin. Bernardi found an increase in the concentration of calcium and potassium in the blood serum following electrical stimulation of the muscle of narcotized dogs.

Although the changes in the concentration of the three inorganic constituents have not been measured on the same animal, it would appear highly probable that the concentration of potassium, calcium and phosphorus rise during a convulsion, and that these changes are a result, and not the cause, of the convulsion.

The effect of previous administration of bromides upon control animals is to reduce the magnitude of the changes, and even to reverse the usual direction of the change in calcium during the convulsion. The administration of bromide does not, however, influence significantly the concentration of calcium or phosphorus, or the ratio of calcium to phosphorus, up to the time of the induction of the convulsions.

Thus, in the series of animals in which there was no operative procedure of any sort, aside from that necessary for the induction of the convulsions, the average ratio of calcium to phosphorus immediately before the injection of camphor or electrical excitation of the cortex was 1.8. This ratio fell to 1.6 after the convulsions.

In the animals to which bromides had been fed previously, the ratio remained at 2 both before and after the convulsions. In the series in which the convulsions were induced by cerebral anemia,

the ratio was 2 and 1.9 respectively, before and after occlusion of the head arteries.

The great bulk of clinical observations on the concentration of calcium, and sometimes phosphorus, in the blood of epileptics has missed the point (1) in not stating with sufficient exactness the relation of the time at which the blood was drawn for analysis to the incidence of the convulsions, and (2) in not stating whether the patient was under bromide or luminal therapy at the time. More observations from the clinical side are needed. In the absence of such observations, one might hazard the guess that the changes in concentration of calcium, potassium, and phosphorus would not be very great, perhaps even within the limits of experimental error, in mild cases in which the convulsions are neither severe nor prolonged, and during bromide and luminal therapy. Changes of greater magnitude might be expected in *status epilepticus*.

A second point of importance is the change in the concentration of calcium and phosphorus following deprivation of the thyroparathyroids.

There is a general agreement that the concentration of calcium in the blood serum falls after thyroparathyroidectomy but the statements in the literature would indicate that there is a less close agreement on the deportment of phosphorus. There is a general agreement, also, concerning the onset of tetany within 48 hours or less, after operation, other things being equal. It is generally stated that the excitability of the nervous system is increased in this post-operative period. But there has been no statement of the mechanism of this change of irritability in terms of chemical mechanics, in this condition or any other. The general vagueness of the term irritability, with its perpetuation of the older vitalistic significance has led to its uncritical use here, as well as elsewhere in biology (Blackman). The appearance of tetany is not dependent solely upon the concentration of calcium, since Bryan and Garrey have shown that in dogs, tetany appears when the external temperature is raised, and ceases when the external temperature is lowered, the concentration of calcium remaining constant. Again, Greenwald insists that if the concentration of phosphorus can be kept low, tetany may not appear even though the concentration of the calcium is within limits where tetany might be expected to appear. One gathers from the literature the general impression that most

investigators look upon the change in hormone action following thyroparathyroidectomy as the driving force or the cause of the subsequent changes in the nervous system. We do not recall that any one has raised the question whether, after all, the central nervous system may not have something to do with the chemical changes which are observed in these animals. In terms of the old Greek pathology, the humors of the body may for some reason or another, independently of the nervous system, undergo changes which react upon the nervous system. We might equally well raise the question whether the nervous system may not have some relation to the state of the humors of the body.

The deportment of animals to which bromide is administered before or after thyroparathyroidectomy may have some bearing on the questions raised above. Bromides do not affect significantly the concentration of the calcium or phosphorus in control animals, but they do affect not only the concentration of calcium and phosphorus, but also the ratio of calcium to phosphorus in animals after thyroparathyroidectomy. Bromides have generally been regarded as drugs which decrease the excitability of the nervous system, and have generally been employed therapeutically as sedatives. The significantly higher concentration of the calcium, together with the relatively lower concentration of the phosphorus in the post-operative period under bromide therapy gives rise to the suspicion that certain processes of metabolism whose rate or magnitude are, in part, at least, under control of the central nervous system, may have something to do with the rate and amount of change of calcium and phosphorus in the post-operative period. The experimental results suggest that bromide therapy might be of some benefit clinically in cases of tetany. One of the most striking results of the whole series of experiments in the prolongation of life and the change in the calcium to phosphorus ratio, without the appearance of tetany, in animals under bromide therapy.

The changes in concentration of calcium and phosphorus during convulsions of experimental origin are in the same direction as those in control animals, and even of relatively greater magnitude so far as the calcium is concerned. The changes in phosphorus are relatively almost as great in controls as after thyroparathyroidectomy, *i. e.*, 36 per cent and 39 per cent respectively. One difference between operated and control animals comes out in the changes

of the calcium and phosphorus during convulsions after bromide therapy. The changes in control animals are, in general, rather small and in the direction of a decrease. There has been an increase in concentration of both calcium and phosphorus even under bromide therapy, in animals in which convulsions were induced after thyroparathyroidectomy.

If we compare the ratio of calcium to phosphorus in animals after thyroparathyroidectomy to the same ratio in control animals, we find a significant difference. In the series of animals in which convulsions were elicited following thyroparathyroidectomy by the intravenous injection of camphor or by electrical excitation of the cerebral cortex, the average ratio of calcium to phosphorus was 1.0 both before and after convulsions. When cerebral anemia was the method used, the ratio changed from 1.0 immediately before the convulsions to 1.2 afterward. In those animals which had been fed bromide, the ratio was 1.4 before the induction of convulsions, and 1.3 afterward. The ratio of calcium to phosphorus tends to fall after thyroparathyroidectomy to about half its value in control animals. When, however, bromides have been administered, the value of the ratio falls much less. In animals which are maintained under bromides, the ratio may even rise, to a value approximating that of the controls.

A third point is that changes in the reaction of an animal to convulsant drugs may occur independently of the changes in the concentration of the calcium and phosphorus. It is well to remember this, since without adducing any other considerations, or showing the presence or absence of other conditions in the animal, the changes in the concentration of calcium and phosphorus have been held to be responsible for the general hyperexcitability after thyroparathyroidectomy. The observations upon the effects of adrenalectomy show that the minimal convulsive, lethal, and total dosage per pound of absinth or camphor are markedly reduced even a few hours after operation. The concentration of calcium and phosphorus in the blood of such animals does not vary significantly, either immediately before the injection of the first dose of the drug or during the period of convulsions, from that observed in control animals. This observation does not, of course, exclude the possibility that the changes in the reaction of animals to convulsant agents following thyroparathyroidectomy are dependent solely upon the

changes in phosphorus and calcium; but they do raise a doubt as to whether this is actually the case. So far as our knowledge goes, no one has estimated (much less excluded), changes in the concentration of epinephrin in the blood or other changes in other endocrine glands in the period following thyroparathyroidectomy. It may be that such changes do not occur following thyroparathyroidectomy, or that, if they do occur, they are unrelated to any of the phenomena rather loosely included under the term hyperexcitability, but these are matters to be determined by experiment, rather than assumed.

SUMMARY.

1. The minimal convulsant and total dosage of a drug necessary to elicit convulsions is much less in cats after thyroparathyroidectomy than in control animals.

2. The number of electrical excitations of the cortical motor area possible in cats after thyroparathyroidectomy is much smaller than in controls.

3. The number of occlusions of the head arteries which can be done in animals after thyroparathyroidectomy is much smaller than in controls.

4. The administration of sodium bromide for two weeks before thyroparathyroidectomy prevents the post-operative appearance of tetany and, if continued, prolongs life for at least three or four weeks without other remedial measures.

5. In cats after thyroparathyroidectomy, the calcium phosphorus ratio is almost 50 per cent lower than in controls; the calcium phosphorus ratio in cats under bromides before operation is, however less changed, and may even approach the ratio of the controls.

6. While there is always a rise in calcium and phosphorus of the blood serum following experimentally induced convulsions, both in controls and after simple thyroparathyroidectomy, previous administration of bromides causes a fall of calcium and phosphorus following convulsions, in both sets of conditions.

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DISCUSSION.

DR. S. BERNARD WORTIS (New York City).—I want to congratulate Dr. Pike for this excellent study. It seems interesting that we should only now be gaining accurate experimental information of the relationship of the greater susceptibility of animals to experimentally induced convulsions due to trauma or glandular dysfunction outside of the nervous system.

Some years ago, Elsberg and Stookey showed that the susceptibility to absinth convulsions was increased following thyroidectomy in cats. Dr. Pike has now shown that this extends also to the parathyroid gland and has very conclusively demonstrated that the calcium-phosphorus fractionation of the blood serum is a product, not the cause, of the convulsive seizure.

I believe that such experimental studies of fits will help to clarify our knowledge in distinguishing between some known causes and many unknown effects of convulsive seizures.

THE EFFECT OF INTERCURRENT CHRONIC PULMONARY TUBERCULOSIS ON THE CONVULSION THRESHOLD IN EPILEPSY.*

A Study of One Hundred Cases.

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Clinical experience indicates that intercurrent acute or chronic diseases very often modify the symptoms of a preexisting disorder, either to ameliorate or aggravate these symptoms depending upon the metabolic and physicochemical changes produced by the complicating illness.

That tuberculosis is a very wide-spread disease and one in which its victims very often suffer from other pathological processes is universally known. That it seems to have an influence upon other diseases in some manner, usually to increase the severity of the preexisting disorders, is also a well-recognized fact. In hypothyroidism tuberculosis is the most common intercurrent disease and is usually the cause of death.[35] Diabetes mellitus often terminates in a tuberculous bronchopneumonia, and pulmonary tuberculosis occurring in a diabetic patient aggravates the symptoms making the treatment much more difficult and the prognosis much more unfavorable.[14] Basabe [2] states that "tuberculosis is the gravest complication of diabetes."

The relationship between epilepsy and pulmonary tuberculosis has not been studied to any extent by investigators in either field of research. Lennox and Cobb,[30] in their excellent work on epilepsy, found that pulmonary infections were a common cause of death in epileptics in institutions, and continued to state that "such infections are a complication rather than a cause of convulsions." However, nothing is said of pulmonary tuberculosis.

In 1930, J. Felsen [12] studied the thorax of 55 epileptics. In 18 of these he found evidences of an active or healed pleuritic or

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pulmonary lesion; five or six were distinctly tuberculous. This leads us to the question as to the possibility of either condition as a predisposing factor to the other. Although no investigations have been made concerning this problem it is the almost unanimous opinion of well-known phthisiologists [43] that pulmonary tuberculosis is not a predisposing or exciting cause of epilepsy. Fishberg [13] states, " I have seen many cases of epilepsy with tuberculous lesions in the lungs or other organs, but the proportion appeared to me to be no more than in those who have no epilepsy." This, I believe, is the consensus of opinion of many working in the field of epilepsy.

Recent investigators [18, 21] found that the effect of an intercurrent febrile disorder on preexisting epilepsy was a decrease in the number of seizures in the majority of cases during the months of illness. This was best demonstrated when the intercurrent disorders were among cases of non-respiratory diseases such as scarlet fever, mumps, etc. In the respiratory group of disorders the change in frequency of seizures was found to be very slight. Also, Hodskins and Guthrie [25] found that the convulsion threshold in epileptics who were suffering from any form of cancer was raised so that a decrease in the number of seizures occurred.

With the feeling that there is no need of justification for a study in a disease as full of mystery as epilepsy, I followed similar methods of investigation in an effort to ascertain the effect of intercurrent active pulmonary tuberculosis on the convulsion threshold in epilepsy.

In the hundred cases of epilepsy presented in this paper all of the patients were suffering from active pulmonary tuberculosis as evidenced by a positive sputum, elevated pulse and temperature, in most cases a loss of weight, and many of the other classical clinical signs and symptoms of activity of tuberculous lesions. The cases represented mostly advanced cases of pulmonary tuberculosis in adults. The average monthly convulsion rate prior to the illness was compared with the number of convulsions occurring during all the months of activity of the tuberculous process. Similarly, this rate was compared with the monthly convulsion rate during the last two months of illness. The average monthly weights were compared in the same manner.

Of the hundred patients here studied 39 were males and 61 were females. Twenty-eight are alive, of whom six are males and 22

are females; of the 72 that are dead, 33 were males and 39 were females. From these observations, it appears that although the incidence of chronic pulmonary tuberculosis among females was almost twice that in the males (36 per cent more), the number of females living was almost four times that of males.

The average period of observation before the onset of the acute illness was 11.4 months, and during the period of activity was 8.3 months. In all of the patients studied, the average monthly rate of convulsions before illness was 10.2; during the period of acute illness the number was 7.1 seizures per month. Similarly, the average weights per month also showed a drop from 111.5 pounds to 102.7 pounds per patient. These figures give a decrease of 30 per cent in the monthly rate of convulsions with an accompanying 8 per cent loss of weight during the stage of the activity of the tuberculous process as compared with the average rate before the onset of the acute illness.

Upon comparing the values found during the 11.4 months previous to the onset of the active pulmonary disease with those occurring during the last two months of illness, we find that it was during the latter months that the greatest drop occurred both in the frequency of convulsions and in the average weight per month—from 10.2 to 5.9 convulsions per month (a 42 per cent decrease), and from 111.5 to 100.3 pounds per patient (an 11 per cent loss of weight). These comparisons can best be realized by referring to Table 1.

Of the hundred cases, 79 showed this decrease in the number of convulsions with an accompanying loss of weight. Among the other 21 patients were 12 cases in which the weight remained the same or was greater during the acute illness although the number of seizures per month decreased. This observation might be explained by the fact that such patients receive more careful attention, especially with regard to diet, rest, and general hygienic care, which, in a patient with a good resistance always tends to increase the weight.

In eight cases, five of which are alive, there was no change or an *increase* in the monthly rate of convulsions during the entire period of active pulmonary tuberculosis with a loss of weight. It is possible that this might be due to the fact that since these patients are more carefully watched during the acute illness all seizures

TABLE 1.*

	Name.	Before illness.			During illness.			During last two mos. of illness.		
		Monthly convulsion rate.	Monthly weight.	No. of months counted.	Monthly convulsion rate.	Monthly weight.	No. of months counted.	Monthly convulsion rate.	Monthly weight.	
1	S.McL.	3.3	112.3	12	2.7	113.0	15	1.0	110.0	1
2	A.M.W.	7.0	103.0	7	6.1	95.2	10	3.0	97.0	2
3	G.N.	2.5	97.0	12	0.5	93.0	12	0.0	83.5	3
4	E.C.	24.0	93.5	12	22.3	92.0	6	19.0	88.0	4
5	I.N.	19.3	107.0	12	14.4	103.4	5	8.0	101.5	5
6	J.D.	24.0	100.0	12	3.0	86.0	12	1.0	87.0	6
7	M.McE.	8.0	64.5	12	6.4	58.0	12	4.0	58.0	7
8	M.C.O'K.	54.0	85.0	12	32.5	85.0	7	42.0	91.0	8
9	M.H.C.	11.0	123.0	12	6.8	119.0	12	5.5	125.0	9
10	N.M.K.	2.4	86.4	13	1.5	83.5	13	1.0	81.0	10
11	A.C.	5.6	69.9	12	4.3	65.4	12	9.0	68.0	11
12	F.P.	6.0	131.0	12	4.3	125.0	12	3.5	112.0	12
13	S.S.S.	4.3	110.0	12	3.5	106.0	10	3.5	103.0	13
14	E.B.	8.0	118.5	12	6.0	115.4	8	6.5	121.0	14
15	S.N.	14.8	87.0	12	9.0	?	5	7.5	?	15
16	C.St.G.	23.5	107.5	12	21.0	107.0	12	23.0	107.5	16
17	H.T.	22.3	91.0	12	7.5	76.7	4	4.0	70.0	17
18	H.M.F.	8.3	105.0	12	3.0	102.0	7	2.5	95.0	18
19	C.F.O'B.	6.5	149.0	12	3.8	135.5	8	2.5	130.0	19
20	G.S.	3.5	79.5	12	2.0	63.0	10	1.5	58.0	20
21	T.McC.	5.7	102.3	12	3.0	95.0	12	4.0	?	21
22	M.F.	10.5	91.7	12	8.9	81.0	10	7.0	?	22
23	A.S.	15.3	96.5	12	12.4	91.8	8	7.5	94.0	23
24	E.B.	16.0	79.0	12	9.5	63.0	8	13.0	60.0	24
25	G.P.	5.5	109.0	12	3.0	102.0	6	0.0	86.0	25
26	M.S.	7.0	129.0	12	0.5	101.3	6	0.0	93.0	26
27	E.M.R.	22.4	132.0	10	14.4	116.0	5	5.0	110.0	27
28	B.L.	2.0	101.0	12	1.7	99.0	10	2.5	99.0	28
29	M.F.	23.0	73.5	12	16.0	75.0	12	10.0	81.0	29
30	A.R.McK.	7.2	69.3	12	7.0	71.5	6	3.0	70.5	30
31	W.W.	7.5	121.5	12	6.0	123.5	12	4.5	121.5	31
32	J.T.	2.3	99.0	12	2.0	107.0	15	0.0	107.0	32
33	N.G.	4.8	82.0	12	1.0	93.0	6	1.0	96.5	33
34	B.C.	5.6	126.0	12	3.0	129.0	6	2.0	139.0	34
35	A.D.	3.0	126.4	12	3.0	103.0	9	2.0	95.0	35
36	C.A.P.	12.8	80.0	12	15.2	68.4	8	8.5	75.0	36
37	A.C.	1.8	132.0	12	2.2	124.7	9	3.0	124.5	37
38	J.B.	4.5	158.3	12	6.0	148.0	12	2.0	145.0	38
39	R.G.	6.0	108.5	12	10.5	103.8	7	14.5	103.0	39
40	M.M.C.	6.0	113.0	12	3.2	111.4	5	2.5	114.5	40
41	G.E.R.	8.0	106.0	12	7.0	99.5	13	8.0	99.0	41
42	Y.P.	59.5	105.2	12	22.0	102.0	12	18.0	110.0	42
43	B.L.M.	2.3	114.0	12	1.8	112.0	5	2.0	109.0	43
44	J.D.	0.3	113.0	6	0.0	101.0	12	0.0	101.0	44
45	E.F.	4.0	73.0	12	3.3	72.5	12	1.0	73.5	45
46	J.B.	2.2	129.0	12	1.9	107.5	12	4.5	107.0	46
47	J.W.	5.0	112.8	10	3.2	106.6	12	2.0	116.0	47
48	A.D.	2.7	107.0	12	1.9	94.0	6	3.5	96.0	48

* This table presents an analysis of one hundred cases showing the relative frequency of convulsions and changes in weight occurring in epileptics before and during an intercurrent active pulmonary tuberculous condition. Numbers 1–39 (inclusive) represents the number of females dead; numbers 40–61, females living; numbers 62–94, males dead; numbers 95–100, males living. Total sixty-one females, thirty-nine males; twenty-two females and six males living; thirty-nine females and thirty-three males dead.

TABLE 1.—CONTINUED.

	Name.	Before illness.			During illness.			During last two mos. of illness.		
		Monthly convulsion rate.	Monthly weight.	No. of months counted.	Monthly convulsion rate.	Monthly weight.	No. of months counted.	Monthly convulsion rate.	Monthly weight.	
49	L.B.	6.0	102.0	12	4.5	101.0	9	1.5	100.5	49
50	J.K.	11.8	95.3	12	7.7	84.2	10	4.5	82.0	50
51	M.S.	16.0	148.0	8	14.0	121.7	7	14.0	118.0	51
52	L.G.	5.0	127.0	9	4.3	109.0	9	3.0	116.5	52
53	E.K.	4.8	98.5	12	3.1	90.0	7	1.5	?	53
54	G.C.	12.1	102.5	9	9.7	98.3	6	7.5	98.0	54
55	A.R.	8.0	120.0	12	7.0	107.8	6	3.5	111.0	55
56	L.C.	6.6	116.5	12	5.5	102.8	9	5.0	95.0	56
57	G.L.	7.6	98.5	8	6.9	79.3	11	7.0	?	57
58	A.K.	5.8	109.0	12	3.5	105.0	8	4.0	109.0	58
59	M.E.C.	4.3	117.5	12	3.2	113.5	8	3.0	114.0	59
60	M.D.	4.3	120.3	12	2.7	120.0	6	3.0	120.0	60
61	I.N.	5.3	99.3	3	4.8	107.4	8	6.5	113.0	61
62	F.J.H.	5.0	109.0	4	2.5	97.0	2	2.5	97.0	62
63	J.F.S.	8.9	124.0	12	3.4	106.0	4	2.5	104.0	63
64	E.M.	8.0	143.0	12	3.5	140.5	8	3.0	140.5	64
65	F.K.	24.3	113.5	12	14.4	94.7	5	15.5	94.0	65
66	G.F.	10.0	124.7	12	3.8	95.0	4	1.5	90.0	66
67	E.D.	21.5	113.0	12	15.3	96.0	11	18.0	85.5	67
68	C.D.	32.3	125.5	12	20.0	114.5	6	13.0	110.0	68
69	D.McC.	7.0	118.0	12	5.5	117.0	6	4.5	113.0	69
70	D.H.L.	4.0	140.0	12	2.0	134.0	4	2.5	132.0	70
71	H.H.	21.0	104.0	12	15.0	101.0	5	3.0	100.0	71
72	J.N.	3.0	113.5	12	2.5	97.0	12	3.0	92.5	72
73	W.C.	6.0	109.0	12	4.0	107.0	6	5.0	107.5	73
74	C.E.B.	22.7	108.0	12	8.5	96.5	8	8.5	86.5	74
75	F.E.B.	11.3	106.0	12	9.0	90.7	4	3.5	78.0	75
76	T.Q.	28.0	98.0	12	26.0	86.0	6	17.5	86.0	76
77	J.J.S.	15.5	161.0	12	9.0	115.0	5	9.6	108.0	77
78	J.H.H.	15.5	115.0	12	3.5	106.5	7	7.0	100.0	78
79	A.O'B.	16.5	126.0	12	4.5	109.5	4	3.0	101.0	79
80	T.C.	5.0	133.5	9	3.0	113.0	5	3.5	115.0	80
81	H.K.	17.5	127.0	12	9.7	119.0	4	9.0	118.0	81
82	W.M.	6.0	102.0	12	3.6	85.0	5	3.0	85.0	82
83	B.P.	5.3	128.3	12	3.4	115.0	7	1.0	108.0	83
84	R.A.B.	11.3	124.5	12	7.3	122.0	9	4.5	119.0	84
85	C.E.S.	4.8	101.3	12	3.0	100.5	8	3.0	88.0	85
86	J.Q.	11.8	157.0	12	8.5	156.5	8	7.5	156.0	86
87	P.H.O.	7.0	122.5	12	3.0	122.0	12	0.5	123.0	87
88	B.A.	7.0	118.0	12	6.0	110.5	6	5.5	110.0	88
89	C.C.C.	46.0	92.0	12	41.0	98.0	12	51.0	94.0	89
90	C.C.S.	7.5	121.0	12	4.3	122.0	6	2.1	122.0	90
91	D.H.	17.3	124.7	12	11.5	118.0	7	6.0	131.0	91
92	N.P.	12.0	134.0	12	16.2	132.0	4	15.0	131.0	92
93	F.McS.	2.7	110.5	12	3.5	111.5	12	2.5	111.0	93
94	G.O.L.	5.6	126.0	12	4.0	120.6	6	5.5	130.0	94
95	C.S.P.	8.0	129.0	12	6.2	115.0	8	8.0	121.0	95
96	H.M.	13.0	47.0	4	1.8	44.0	5	1.0	48.0	96
97	K.B.	8.0	105.0	12	8.0	93.0	6	5.0	93.5	97
98	P.DiM.	8.0	146.0	12	3.0	138.5	7	2.0	135.5	98
99	E.B.	5.5	127.0	12	2.5	107.7	12	1.5	102.5	99
100	H.B.	14.3	113.3	7	15.0	85.0	6	9.5	75.0	100
	Averages	10.2	111.5	11.4	7.1	102.7	8.3	5.9	100.3	

are recorded more faithfully. However, in five of these eight cases there *was* a decrease in the number of convulsions during the last two months of the active tuberculous process.

In one of the 21 cases there was an increase both in the number of convulsions and in the weight during the active illness.

Thus, during the acute stages of the intercurrent pulmonary tuberculosis, which averaged 8.3 months, there occurred a noticeable decrease in the convulsion rate in 91 of the 100 cases, ranging from 0.3 to 37.5 convulsions less per month. In five more cases there was a diminution in the number of seizures only during the last two months of acute illness, making a total of 96 out of 100 cases.

Table 1 represents an analysis of the hundred cases. It is to be noted that the largest number of seizures per month before the intercurrent illness set in was 59.5 and the least was 0.3. The largest number occurring during the illness was 41 and the least 0 seizures per month. Five patients had no convulsions at all during the last two months of illness, whereas for the 11.4 months previous to their illness they had 0.3 to 7.0 seizures per month.

I might add that in the 22 cases that are still living, the frequency of convulsions has resumed the same level as before the acute illness; thus, no permanent or prolonged beneficial effect has resulted.

The demonstration that changes in the physicochemical processes in the body may greatly modify seizures was, according to Lennox and Cobb,[30] the most distinguished advance made in the knowledge of epilepsy. With this thought in mind, I sought a biochemical solution as a possible explanation for these findings.

In the various procedures that aim to control the number of seizures, either to arrest them or to reduce their frequency, the essential feature is dehydration, and to a lesser extent, acidosis.[11, 16, 48] For example, we have the starvation treatment, the limitation of water intake, the induction of fever, the ketogenic diet, etc., all having virtually the same effect—dehydration. Hodskins and Guthrie [25] assume that dehydration accompanies any chronic wasting disease and state that "upon this may depend important physiologic and physicochemical changes."

It is clear that during the activity of the tuberculous process there are fever, night sweats, anorexia, and loss of weight. From

this one might consider dehydration as the underlying principle in favorably influencing the number of convulsions.

Investigation [50] seems to indicate that, contrary to the general belief, analyses of the tissues of the tuberculous cadaver have actually shown that the proportion of water is increased as compared to the amount in the normal tissues. This is explained by an investigator who states that there is a decrease in the tissue protein due to toxicogenic destruction with an increase in the proportion of water and fat, a change which is usual in all wasting diseases.

Also, Brieger [5] found that there was no concentration of the blood in chronic pulmonary tuberculosis, but in advanced cases with increased serum protein, the plasma volume was increased. Pycnometer determinations of specific gravity of the blood by Strasser [46] gave consistently low readings for advanced tuberculosis like those of cardiac dropsy and nephrosis. Other investigators obtained similar results.

F. B. Byrom [6] in a study of the exchange of water, sodium, potassium, and nitrogen in epilepsy concludes that "the epileptic convulsion is not directly conditioned by the degree of hydration of the tissues," but may be due to some derangement of the water—electrolyte balance and the various electrolytes of the fluids within or around the neurone. H. M. Keith [29] found that limitation of fluid intake for a long time did not reduce the susceptibility to convulsions, whereas rapid dehydration by means of intravenous administration of 50 per cent sucrose did do so. According to H. Hopkins—Detrick [27] the basis of the starvation treatment, induction of acidosis and dehydration, is the readjustment in electrolytic balance.

Since these findings seem to indicate that dehydration is not an essential feature in chronic pulmonary tuberculosis, and that it alone does not entirely explain the mechanism of the effect of the various methods of treatment in epilepsy, I investigated the general metabolic changes that might occur in each condition.

Basal metabolism studies in epileptics have given us some very interesting data. Most of the early investigators found that the majority of adult patients with convulsions had either a normal or a reduced rate of oxygen consumption. Later evidence (1929-1932) seems to indicate that the basal metabolism in these patients

is *definitely* decreased. T. K. Davis,[8] in his series of cases, obtained results which suggested to him that " patients subject to convulsive seizures tend to have a basal metabolic rate lower than normal." Felson,[2] in in 1930, found a low metabolic rate in most of his cases and a lower percentage of high basal rates among epileptics than normals. LeGrand A. Damon [7] made 350 basal metabolism tests of epileptics at the Craig Colony and obtained some very interesting information. He found that 50 per cent of the patients tested showed abnormal basal metabolic rates with the chances of 2:1 that the rates would be low rather than high. He also found that the lower the convulsion threshold in these patients, that is, the greater the number of seizures, the greater the percentage of low metabolic rates. It is to be noted that rates of minus 10 to plus 10 were considered by Damon as normal values which, according to Trumper and Cantarow,[49] represent the strictly normal range.

It is possible that the metabolic rates obtained in epileptics confined to institutions may not be representative of the vast majority of epileptics at large. The oxygen consumption of the institutional patient might be somewhat reduced because of the sedentary life that he leads. This fact cannot materially affect the low rates obtained by most recent observers, for metabolic rates are generally recorded when the body is at complete mental and physical rest, and no correction is made for the kind of occupation of the individual in calculating basal rates. Again, even following the administration of morphine, the metabolic rate may be only slightly diminished.[49] I therefore believe that the low basal metabolic rates found by many observers in at least 50 per cent of epileptics ought to be accepted as representative values.

As in practically all fevers the basal metabolic rate in active pulmonary tuberculosis is increased, although the rise is relatively less than in other febrile disorders. McMahon and Klein [36] found a definite increase, especially in the advanced stages of the disease, the degree of elevation being dependent upon the severity of the case. Williamson,[51] in 1929, and Peterson and Levinson,[42] in 1930, found very similar results. Many other studies have corroborated these observations, and most clinicians advise a much higher caloric diet because of this increased metabolism. There is, therefore, the possibility that this increase in the basal metabolic rate in epilepsy during an intercurrent active tuberculous condition, and, I venture

to say, in any acute or chronic febrile disorder, might be responsible for the decrease in the number of seizures during the active illness. Since the thyroid gland is essentially normal in the tuberculous individual,[50] I do not believe that any endocrine readjustment, even of temporary nature, occurs during this period of acute illness so that the underlying mechanism involved is still not quite clear.

It has been observed by Talbot,[48] Joslin, and others that the coexistence of epilepsy and diabetes is rare. Hodskins [26] noted but one case of diabetes in about 6325 epileptics at the Monson State Hospital and found that there was a remarkable decrease in the frequency of convulsions after the diabetic condition had developed in this patient. The development of ketosis, dehydration, and other metabolic disturbances in the diabetic was suggested as the cause of this beneficial effect upon the severity of epilepsy. Also Hodskins and Guthrie [25] observed a decrease in the frequency of seizures in most of their cases of malignancy complicating epilepsy. They believe that hyperglycemia, which is generally associated with cancer, may have been a factor in influencing the convulsion threshold so that there was a decrease in seizures.

MacLean and Sullivan,[32] in 1926, when studying so-called status lymphaticus from the blood sugar angle, observed low blood sugar levels within a half hour of death in three patients in convulsions. In the same year, Josephs [28] ascribed convulsions occurring so frequently in infants and children, especially at the onset of acute infections, to starvation *hypo*glycemia. Griffith,[20] in 1929, reported a series of cases of convulsions associated with hypoglycemia occurring in children. McGovern observed attacks of amnesia and coma accompanied by convulsions during which the blood sugar content fell to 30 milligrams per hundred cubic centimeters. Administration of dextrose intravenously relieved the acute convulsive state, and carbohydrates given every hour during the forenoon kept the patient free from attacks for about a year and a half. J. B. Sears,[45] in April 1933, described two cases of convulsions occurring during late ether anesthesia one of which recovered coincident with the intravenous injection of 20 cubic centimeters of 50 per cent dextrose. S. Harris,[22] in 1933, reported three cases of true epilepsy associated with hyperinsulinism, and suggests a possible relationship between the two. These are, of course, exceptional cases. Also Lennox and Cobb [30] state that "artificially

induced hypoglycemia in epileptic patients may assist in the induction of seizures."

Thus we have noted the absence of convulsions or their diminution in conditions where hyperglycemia (hypoactivity of the pancreas) is an important clinical feature, and the presence of convulsions in hypoglycemic states (hyperinsulinism, etc.). It would, therefore, seem reasonable to believe that, whatever the underlying principle may be, an intercurrent disorder in which the blood sugar is elevated would tend to relieve the symptoms of epilepsy.

Investigation of the carbohydrate metabolism in cases with pulmonary tuberculosis indicates important alterations. Berg [3] found that the fasting blood sugar in tuberculosis averaged 10 per cent above the normal average. McBrayer [38] observed an increase in the blood sugar accompanying a rise in basal metabolism rates of over 10 per cent in about one-third of his cases. Ginsberg,[17] in 1929, found an increased blood sugar in 70 per cent of his cases of pulmonary tuberculosis. Peters and Van Slyke [41] state that "in a large proportion of cases with tuberculosis of the lungs the fasting blood sugar and the alimentary glycemia curves are higher than normal." Trumper and Cantarow [40] believe that an increase in the level of blood sugar may be the result of conditions such as fever, nephritis and dehydration, and continue to state that "occurring in association with other factors their influence may be significant."

According to the observations of Gray and Pickinson [19] the function of the pancreas is decreased in toxic states of tuberculosis. This fact, together with the observation that damage to the liver, which occurs in advanced tuberculosis,[1] reduces the capacity to utilize carbohydrates, seem to indicate that in all probability hyperglycemia does occur in active pulmonary tuberculosis.

It is, therefore, possible that the presence of an abnormally high blood sugar, together with other factors in the epileptic patient with intercurrent active tuberculosis, may be at least one of the factors in reducing the rate of convulsions in epilepsy. I do not infer, however, that increasing the blood sugar of all epileptics will have a similar effect, for the administration of carbohydrates in the uncomplicated case of epilepsy usually tends to cause a retention of fluids and not unusually an increase in the frequency of convulsions. These seemingly paradoxical situations can be

explained in that in the tuberculous epileptic we have a diseased condition in which there are many other factors such as possible ketosis, and other general metabolic disturbances to be considered, whereas, in the usual case of epilepsy, these other factors do not exist.

Since the introduction of such methods as the starvation diet, ketogenic diet, ingestion of acid forming salts, such as calcium or ammonium chloride, etc.,[31] in the treatment of epilepsy, much attention has been given to the subject of mineral metabolism. Most observers find that during the interparoxysmal period the blood calcium is within normal limits.[30] The concentration of calcium ions in the blood appears to be dependent upon several factors, one of the most important being the hydrogen-ion concentration.[49] Acidosis or ketosis, either or both of which occur in the starvation diet and dehydration by water intake reduction, is accompanied by a marked rise in available calcium ions due to a readjustment in electrolytic balance. With this in mind Hopkins-Detrick [27] has administered to his epileptic patients potent extracts of parathyroid gland, together with calcium salts. The author found that there was improvement in the general physical and mental condition with a disappearance of convulsions.

That there are no marked deviations from the normal in the calcium content of the serum of patients in various stages of pulmonary tuberculosis was the consensus of opinion among the earlier investigators. However, Ellman,[10] in 1929, found that in tuberculosis the parathyroid gland shows definite histological evidence of increased function. Heuer and Andrus [24] found that reduction in the respiratory area, which occurs in pulmonary tuberculosis caused a fall in the oxygen and an increase in the CO_2 content of the arterial blood. According to Trumper and Cantarow [49] hypercalcemia of mild degree is found in such conditions, which enhance the capacity of the blood for maintaining calcium in solution. Also McCann [34] states that more calcium is required for maintenance of equilibrium in tuberculous than in normal subjects. It is, therefore, possible that the beneficial effects of active pulmonary tuberculosis upon the seizures in epileptics may be due to the hyperactivity of the parathyroid gland with its tendency to increase the ionized calcium in the blood.

Many studies have recently been made to determine the relationship of the fluid constituents of nerve tissue, especially of the brain cells, and the convulsion threshold in epilepsy. Membrane permeability to the electrolytes has been investigated especially by McQuarrie *et al.*[37] His work in this field leads him to favor the view that the mechanism for regulating permeability of the brain cell membranes is defective in epileptics.

Lennox and Cobb[30] found a normal concentration of sodium chloride in the blood plasma and in the spinal fluid, and a normal ratio between the chlorides of these two fluids suggesting a normal relationship between the concentration of sodium chloride in the tissues and blood in epileptics. They also found that fasting or a salt poor diet *reduced* the sodium chloride of the blood of patients, with a coincident reduction in seizures. Another investigator[18] working along similar lines concluded that the reduction of chlorine ions in the fluid constituents of the body was the important factor in reducing seizures. McQuarrie[38] believes that in the adult epileptic there is an abnormal tendency to *retain* sodium chloride, the excess very likely being stored up in the integument. Later literature on this subject indicates that the rise in the convulsion threshold is not due to a decreased plasma chloride alone but is intimately related to a shift in the electrolytic balance between the sodium and chlorine ions in the extracellular fluid and the potassium ions of the intracellular fluid (of the brain cells) *with* an alteration in the net water balance and a deficient cell membrane permeability. There are no data as to the relationship of the electrolytes in the intracellular and extracellular fluids in individuals suffering with chronic pulmonary tuberculosis, but most investigators[4, 47, 49] found a constantly low blood chloride especially in the advanced cases. Muller and Quincke,[40] in 1928, report finding less than normal blood chloride in 21 of 30 cases. That this decrease in blood chloride may be another factor in alleviating the clinical symptoms in epileptics during an intercurrent active pulmonary tuberculosis might well be considered, but that it alone cannot fully explain the beneficial effect must also be kept in mind.

Comparisons of the blood pictures in epilepsy and in chronic pulmonary tuberculosis show some similarities as well as differences. Felsen[12] found a prolonged coagulation time in epileptics, although Lennox and Cobb[30] accept the statements of earlier in-

vestigators, Thom and Wuth, that the coagulation time is normal. Felsen also found a low platelet count, and a moderate lymphocytosis (in 11 of 56 cases). Most investigators found an increased rate of sedimentation of red cells in from one-third to one-half of their cases of epilepsy. This latter fact agrees with the increased fibrin content of the blood in patients observed by Lennox and Allen (1928). The urea nitrogen, non-protein nitrogen, uric acid, and creatinine values of the blood Felsen and others found to be normal.

In pulmonary tuberculosis most observers [50] find that the coagulation time is not markedly altered despite the fact that there is usually more or less increase in the amount of fibrinogen in the blood. The speed of sedimentation is increased in tuberculosis in direct proportion to the rate of progress of the disease, even in afebrile cases. The values of urea, uric acid, non-protein nitrogen, and creatinine of the blood are with few exceptions usually within normal limits, with a tendency to rise in the advanced and acutely ill tuberculous patients. Blood ammonia is increased in proportion to the advancement of the disease.

Low blood cholesterol values have been noted by several investigators [44] preceding the epileptic seizure. Trumper and Cantarow [49] state that the "low plasma cholesterol values have also been reported *during* epileptic seizures," and Pezzali [41] has even suggested the therapeutic administration of cholesterol in epilepsy having observed a fall in the blood cholesterol during epileptic seizures. Similarly, hypocholestemia has been found by several investigators [9, 23] to occur in pulmonary tuberculosis in which condition it appears to be related to the severity of the process.

In epilepsy the hydrogen-ion concentration of the blood is usually normal, but the P_h values of the blood seem to show that within these normal limits "there is an unusual degree of fluctuation from day to day with a tendency to approach a more alkaline reaction.[50] In direct contrast, in pulmonary tuberculosis there is a tendency toward a decrease in the alkali reserve as the case advances. Since the alveolar ventilation is decreased in tuberculosis, there is an increase in the carbonic acid content (CO_2 tension) of the blood. This situation together with the increase in the lactic acid content of the blood that occurs in patients with active pulmonary tuberculosis are important in producing the tendency to aci-

dosis, although at no time is there a marked "acidosis." [50] Since measures which produce primary alkali deficit appear to be of benefit in epilepsy [30, 39] it might be suggested that the increase in the CO_2 tension and lactic acid content of the blood, and the decrease in the alkali reserve, such as occurs in active pulmonary tuberculosis, may have been the important factors in reducing the number of seizures in the tuberculosis epileptic.

We have reviewed the evidence that the tendency of an intercurrent active pulmonary tuberculous process upon the epileptic individual is to reduce the number of convulsions per month. From a clinical point of view, the most important feature to be pointed out is that an increased basal metabolic rate, hyperglycemia, an elevated blood calcium, a reduced blood chloride, and a tendency to acidosis—which is usually of the compensatory type—contingent to active pulmonary tuberculosis, may all be factors which probably raise the convulsion threshold in epilepsy accounting for the decrease in the frequency of seizures.

SUMMARY.

1. Investigation seems to indicate that epilepsy does not predispose to chronic pulmonary tuberculosis, nor vice versa.

2. In a series of one hundred cases of epilepsy with intercurrent chronic pulmonary tuberculosis in its active stages, the frequency of seizures was markedly decreased in the majority of cases, with a demonstrable loss of weight.

3. A review of the literature reveals the following:

(a) That there is a reduced basal metabolic rate in epilepsy and a definitely increased rate in pulmonary tuberculosis.

(b) That convulsions are often absent in diseases with a high blood sugar such as diabetes and cancer and that hyperglycemia tends to occur in the tuberculous individual.

(c) That a normal blood-serum calcium is usually found in epilepsy and that it is often found to be elevated in pulmonary tuberculosis.

(d) That a reduction in the sodium chloride of the blood of epileptics often reduces the frequency of convulsions and that a constantly low blood chloride is often found in patients with active pulmonary tuberculosis.

(e) That comparisons of the blood pictures in epilepsy and in pulmonary tuberculosis show the occurrence of hypocholestemia and an increased rate of sedimentation of the blood in both conditions.

(f) That the P_h values of the blood seem to indicate a tendency in the epileptic to approach a more alkaline reaction, and in the tuberculous patient a more acid reaction.

4. From the above data suggestions are made as to the mechanism involved in active chronic pulmonary tuberculosis in raising the convulsion threshold in preexisting epilepsy so that the frequency of seizures is noticeably reduced.

5. The multiplicity of possible solutions is itself proof that no satisfactory single solution can be found at the present time.

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DISCUSSION.

DR. W. G. LENNOX (Boston, Mass.).—Mr. Chairman, I certainly think somebody ought to congratulate Dr. Karlsberg for this very excellent presentation of material, and for the judicial attitude which he has maintained towards his evidence. The high mortality in tuberculosis in institutions for epileptics certainly is a striking fact. At Craig Colony 12 per cent of all deaths are due to tuberculosis, and there is a corresponding percentage at Monson State Hospital. This might appear of significance except that there is also a high rate from tuberculosis in institutions for the insane. Apparently it is a matter of the institutional life and not of the disease.

I believe that Dr. Karlsberg should make for comparison a curve showing the numbers of seizures in patients without tuberculosis. Hodskins and Yalovlev

showed that with the passage of time there is a tendency for the patients to show more signs of Parkinson's disease and to have fewer seizures. In order to demonstrate that improvement is not a matter of continued residence in the institution, the speaker ought to have a control series. I have observed that it takes a larger dose of a convulsant drug to give a weak, emaciated rabbit a convulsion than it takes for a normal rabbit. Unscientific as it sounds, the sick tuberculosis patients may be just too weak to have a convulsion.

THE AMYLOLYTIC ACTIVITY OF THE FECES IN EPILEPTICS.*

By L. A. DAMON, M. D.,
Pathologist, Craig Colony, Sonyea, N. Y.

During the past few years the attention of those interested in epilepsy has been directed toward the effects produced by the high fat diet and recently to the results obtained by restricting the intake of fluids. In attempting to interpret the improvement produced by these measures, little attention has been given to the effect on the digestive organs with the concomitant chemical changes incident to the metabolism of these diets. Having in mind the possibilities that the results obtained with the high fat diet might be due to the elimination of the carbohydrate from the diet rather than the effect of the ketosis produced, an attempt has been made in this study to determine the ability of the epileptic to metabolize carbohydrates as indicated by the amylolytic activity of the feces.

In a search of the literature on the subject of pancreatic amylase, one interested in epilepsy is struck by the fact that nearly all workers are in agreement that this secretion of the pancreas is markedly stimulated by a diet high in carbohydrates. Okada [1] and his co-workers, in studying the secretory mechanism of the digestive juices, concluded that carbohydrate stimulates the secretions of the pancreatic enzymes through stimulation of the autonomic nervous system. Hawk [2] in carefully checked experiments, indicated that the pancreatic secretion as evidenced by the increased amount of amylase in the stools was stimulated by the ingestion of increased amounts of water and that the reverse was true when the water was restricted. He concludes that this is brought about in two ways: first, a direct stimulation of the nervous mechanism of the pancreas brought about while the water is still in the stomach and, secondly, an indirect stimulation brought about on the entrance of the increased volume of acid chyme into the duodenum. These

*Read at the eighty-ninth annual meeting of The American Psychiatric Association, Section on Convulsive Disorders, Boston, Mass., May 29–June 2, 1933.

findings are of interest in view of the results of water restriction in the treatment of epilepsy and is one of the effects of dehydration that has apparently been overlooked.

The toxic theory of essential epilepsy cannot be dismissed simply because we have not as yet been able to isolate the toxin or discover the means by which it is brought about or the organ at fault. The indisputable fact remains that other recurring convulsions are of toxic origin such as those seen in uremia, eclampsia, alcoholism and following the ingestion of other poisons. Although one can justly criticize the term "autointoxication," it seems to be the only one we have at present which adequately describes conditions often seen in the epileptic and which we have learned to combat in our endeavor to treat the disease. Frequently in cases of status and serial seizures, the only medication required is a thorough cleansing of the intestinal canal. Banting [3] of Toronto and his associates studied the enzymes of the stools in intestinal indigestion and found that in this condition the pancreas fails to produce its normal quantity of these substances. Likewise, Marabito [4] found that in infants with dystrophy associated with septic conditions, in those with food intoxication and in those with chronic indigestion, the amylolytic power of the blood and urine is decreased. That the blood and urine amylase and that found in the feces are parallel has been demonstrated many times.

The feasibility of drawing blood from a vein every day for an extended period is, for obvious reasons, out of the question, hence the necessity of selecting the feces for this study.

From time to time there have been reported in the literature cases of epilepsy that have been apparently benefited by partial resections of the pancreas. Recently Harris [5] reported three such cases and was inclined to credit the relief of symptoms to a correction of a dysinsulinism. Another effect of this procedure would also be a lessening of the amount of the other pancreatic enzymes secreted and should not this factor also be considered.

The method adopted for this study was Hawk's modification of Wohlgemuth's method. To explain briefly, 2 grams of feces were very accurately measured in a mortar, 8 cc. of a buffered normal saline solution was added, 2 cc. at a time, rubbing the fecal mixture to a homogeneous consistency after each addition of the extraction medium. The mixture was allowed to stand for one-

half hour. This constituted a neutral fecal suspension properly buffered to insure maximum action of the enzyme. The suspension was transferred to a 15 cc. graduated centrifuge tube and made up to 15 cc. with the buffered chloride solution, centrifuged for 15 minutes to secure satisfactory sedimentation, the supernatant mixture removed to a volumetric flask and diluted with the phosphate-chloride solution to 50 cc. Into a series of test tubes, varying amounts of this fecal extraction were pipetted, ranging from 3 cc. to one-half cc. each succeeding tube in the series containing 2/10 of 1 cc. less than the preceding one. All tubes were then filled to the 3 cc. mark with the chloride solution in order to maintain the same electrolytic concentration. Five cc. of 1 per cent soluble starch solution were added to each tube and they were placed in the incubator at 38° centigrade for one hour. At the end of that time the tubes were removed and filled with ice water and 1 drop of tenth normal iodine solution added to each. The degree of amylolytic activity could be determined by the blue color which the iodine produced on undigested starch. The last tube in the series which showed entire absence of blue color indicated that the starch had been completely transformed into dextrose. Early in the experiment, tests were performed on freshly passed feces and on feces kept for varying periods and it was found that the amylolytic activity for a given stool did not decrease until after the third day.

The patients selected were of the higher type mentally, in order to secure the best cooperation, and having no known organic basis for their epilepsy. They were all hospitalized in the same ward and received the same diet. In so far as possible this was standardized to contain approximately 50 grams of proteins, 40 grams of fat and 200 grams carbohydrate per day. One-half of the cases were taking luminal in varying doses at the time and this was not discontinued. Accurate observations regarding seizures were made by nurses in constant attendance.

Twenty cases of epilepsy, one of myoclonus epilepsy and eight cases of psychoses without convulsive manifestations have been studied to date. The data obtained covering, as it does, the daily variations in the amylolytic activity of each individual stool, does not lend itself to a generalized grouping and, therefore, is presented for each case for the period which it was under observation. For purposes of comparison, the same diagrammatic scheme has been adhered to throughout the series.

The vertical column designates the amount of fecal extract in each tube of the series and the curve connects the daily reading of those tubes where starch digestion ceases. Therefore, the higher the curve the less fecal extraction was required to digest the amount of starch and hence indicates a greater percentage of amylase. The days on which seizures occurred are represented by a black square above the corresponding date.

Represented in Chart 1 are five cases in which, apparently, the seizures occurred at the high point of amylolytic activity. Obvi-

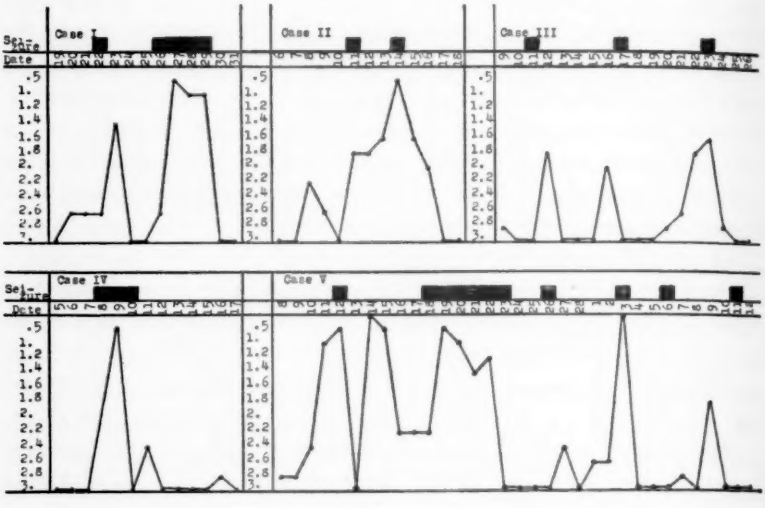

CHART 1.

ously, in interpreting the results allowance must be made for the time consumed in the passage of the feces through the intestinal canal so that the amylolytic activity of a given stool may represent the activity of the pancreas at a time 24 hours preceding its determination.

In Chart 2, four cases are presented which do not seem to show the exact relationship between the high point of amylolytic activity and the seizures as in the preceding chart. However, it will be noted that a greater share of the seizures occurred at this time.

Cases X and XI as shown in Chart 3 and which were observed over a period of nearly two months, show less correlation of these two factors than in the preceding cases.

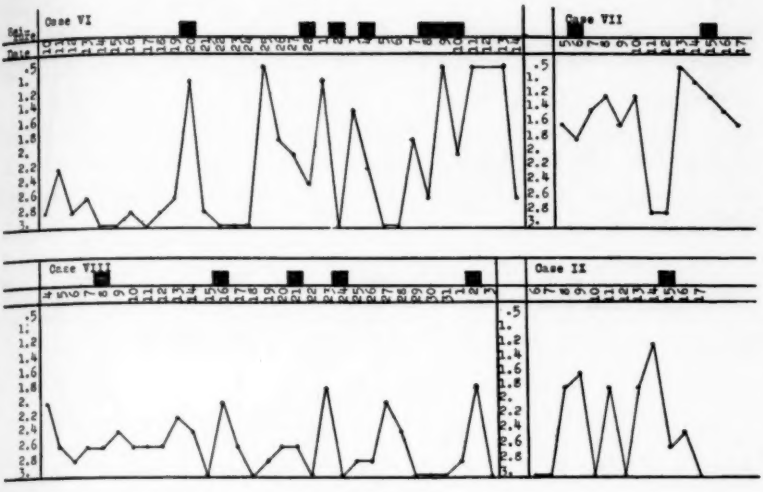

CHART 2.

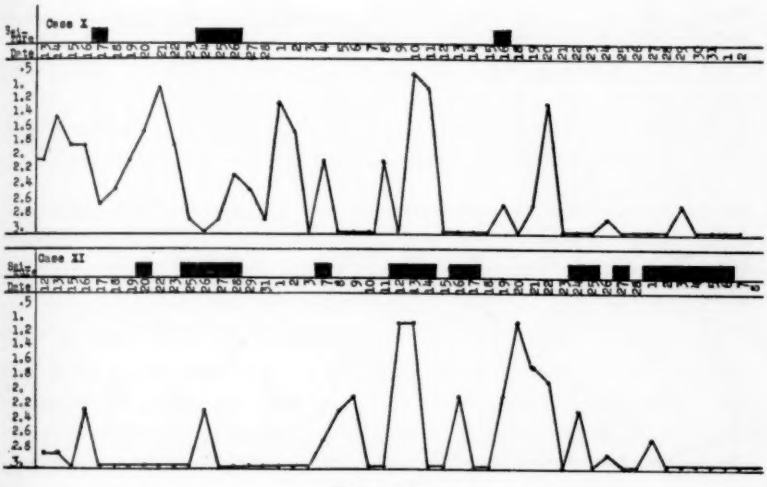

CHART 3.

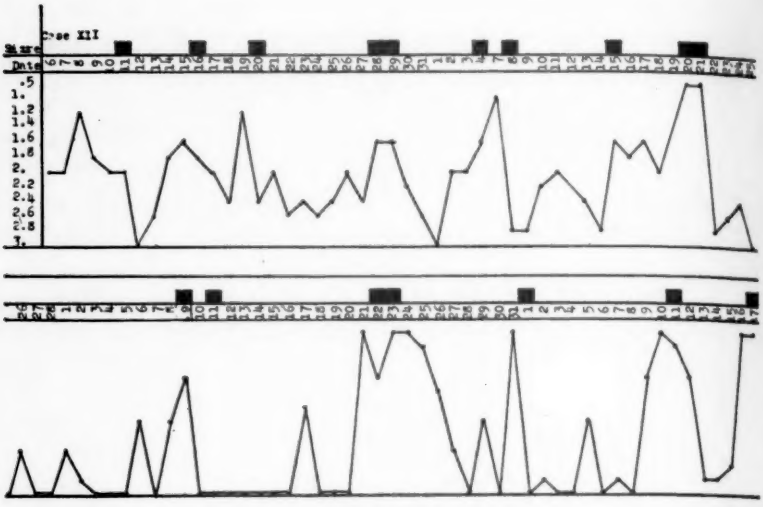

CHART 4.

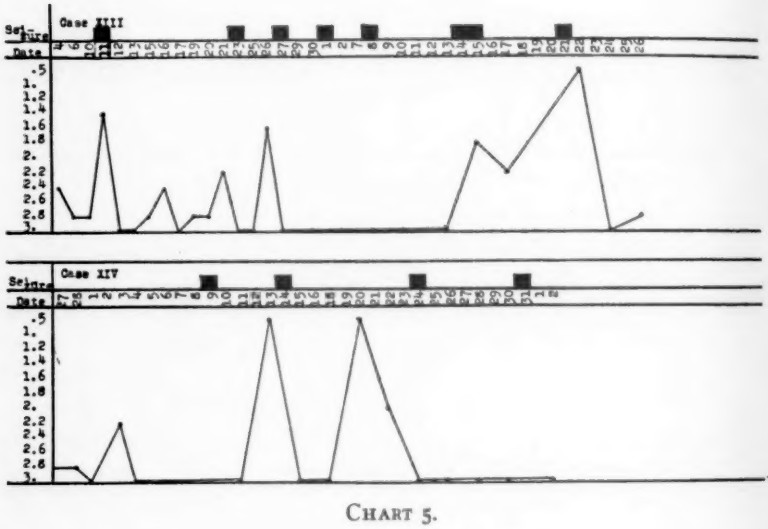

CHART 5.

Chart 4 represents a total observation period of 104 days on one patient. It will be noted that there is a marked similarity between the peaks of amylolytic activity and the occurrence of seizures throughout the entire period.

In Chart 5, I have represented two cases in which constipation was a marked factor. As will be noted there were several days in sequence when no stools were obtained. Therefore the curves cannot be considered as giving a true indication of the amount of this enzyme present at the time of each seizure but it does show the marked variation which is present in epileptics.

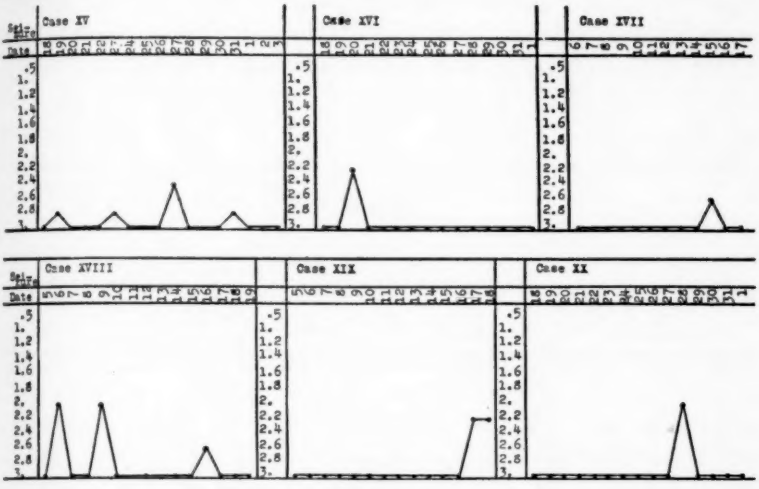

CHART 6.

In Chart 6, I have grouped six cases which were under observation for periods varying from ten days to two weeks and which had no seizures of any kind during that period. These cases were those having remission of seizures or in whom seizures occurred at very infrequent intervals. One is at once struck by the flatness of the curves, none of the time going beyond the sixth tube. Apparently in this series the activity of the pancreas was stabilized as represented by the amount of amylase appearing in the stools.

In Chart 7 is shown the marked variation in the amylolytic activity in the stool of a case of myoclonus epilepsy. This observation was continued over a three months period and from actual observation and reports by the patient himself, and the attendants,

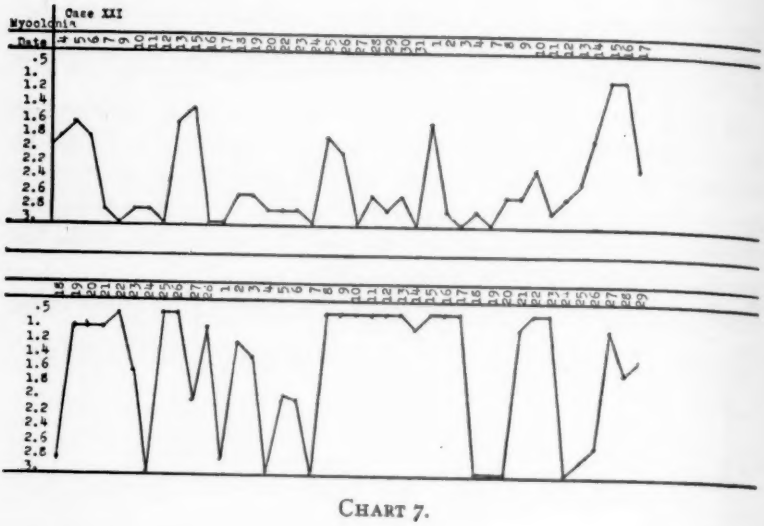

CHART 7.

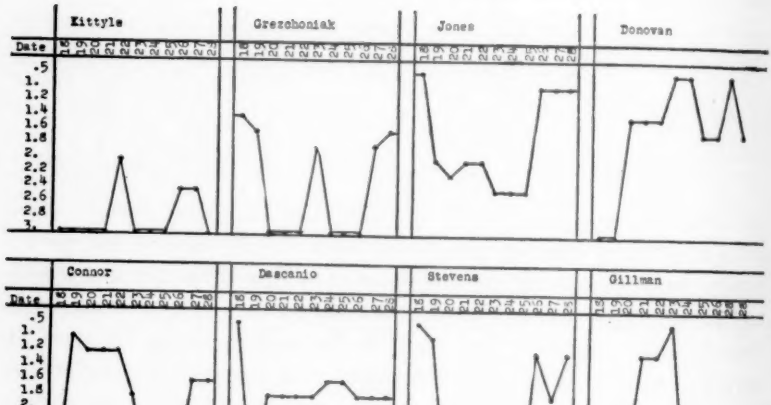

CHART 8.—Psychotic Group, Non-Epileptic.

it was quite remarkable to what extent the high point in this chart corresponds to the days on which he was afflicted with myoclonia. As can be noted in the lower half of the chart a particularly high point occurred from the eighth to the seventeenth. At this time the myoclonia was so severe as to confine him to bed a part of the time.

A search of the literature for a similar series of tests on normal individuals failed to give any corresponding tables for such a group. Todd and Sanford [6] reported a series of tests performed on healthy medical students in which it was found that the amyolytic activity of the feces was from the ninth to the tenth tube. As I was unable to secure normal controls a group of eight psychotic cases, without convulsions, from the Rochester State Hospital were studied in the same manner over a period of ten days. The results are shown in Chart 8. Although variations are as marked as in the epileptic group, the curves are not as abrupt and the general average of reactions seems to be somewhat higher. These should not be interpreted as normal controls.

Any attempt to draw conclusions from this small group of patients would be dangerous, but, nevertheless, there seems to be a direct relationship between the seizures and the amount of amylase present in the stool. In the total epileptic group there were 71 seizures occurring at the high point of amylolytic activity or directly before or after, while only 20 attacks occurred during the low period. The fact that the curves were so low in the seizure-free group of epileptics also adds argument to the possibility of this particular enzyme being the precipitating factor of the convulsion or, at least, its appearance in the stool in increased amount is an indicator of an impending convulsion. In fact, in Case 12 of this series, we were able, with great regularity, to predict the occurrence of a seizure by the increased amylolytic activity of the stool. In searching for a possible explanation for this apparent toxic effect of amylase, I find that Wells [7] in his book on Chemical Pathology has suggested the close relationship between enzymes and toxins. To quote his statement in full: "Enzymes behave in many respects like the toxins both in their manner in acting upon other substances and in the reaction they produce when introduced into the bodies of animals. There is abundance of evidence of a toxin-like structure from the numerous observations on the formation of zymoids which can neutralize anti-enzymes although no longer

active as enzymes." Among others who have suggested the close resemblance between enzymes and toxins are Moore,[8] Dick [9] and Coca.[10] The latter demonstrated that cobra venom is a lipase.

I believe that the results of the experiment demonstrates the necessity for further research along this line. Tests should be conducted on a group of patients that are on the ketogenic diet and also the effects of water restriction on the amylolytic activity in epileptics should be investigated. A method should be used that will more accurately indicate the time of the secretion of the enzyme and thus eliminate the unknown factor of the time elapsed in the passage of the feces through the intestinal canal. This could be done by duodenal tube in cooperative patients. The other enzymes such as trypsin and steapsin should be similarly studied. Therapeutic tests of various enzymes are also indicated.

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DISCUSSION.

Dr. Paul I. Yakovlev (Palmer, Mass.).—I found the paper of Dr. Damon very interesting in that there is evidence of some amylolytic ferment disturbances in his cases, some of which were myoclonus cases. And as he has perhaps observed in the literature, one finds several examples where pathological examination of the nervous system showed evidence of intracellular amyloid bodies, so called, in the brain. There possibly may be some connection be-

tween these abnormalities in the function of the amylolytic ferment and these deposits as found in the central nervous system.

DR. DAN S. RENNER (Skillman, N. J.).—Dr. Damon suggested to me several years ago that he was convinced that the pancreas was playing a part in convulsive disorders. I agreed with him because I didn't know whether it was or not. I am not sure, and he doesn't demonstrate, whether these conditions that he has described are the cause of epilepsy or the result of convulsive disorders. By comparing with the other psychotic cases, I am inclined to think that they really aren't so much a producer of convulsions as of some mental disturbance. I think however that this work offers a new lead, and while it is in its infancy I certainly appreciate Dr. Damon's effort and stimulus in pointing out a new road for investigation.

DR. W. G. LENNOX (Boston, Mass.).—As the speaker said, further observations should be made. I am not terribly impressed with the coincidence of the peaks of excretion with the seizures, because there were so many instances in which that did not occur. Yet if there is such a marked variation from day to day, whether or not seizures are present, this in itself would be of significance. Only there must be some control experiments with normal individuals. The speaker said he was unable to secure such control material. I would suggest that he himself would make a good subject. I have had to use that method in my own studies a good many times.

Abnormalities in the ferments of the body have been reported by European authors, and the matter needs to be run to earth.

RELATION OF PREMATURE BIRTH AND UNDERWEIGHT CONDITION AT BIRTH TO MENTAL DEFICIENCY.

By AARON J. ROSANOFF and CHRISTINE V. INMAN-KANE.

I. Theoretical Introduction.

It has been pointed out many times in the past fifty years or more that studies of twins may throw light on the relative importance of hereditary and environmental factors in human achievement, in intelligence, in temperament, in behavior, in health and disease, and in connection with other human problems.

In the hope of gaining some more exact knowledge of the etiology of mental disorders, we undertook about three years ago to collect records of cases of mental disorders in twins. Our object was to accumulate for each important clinical group an amount of this kind of material that would make possible a statistical treatment.

In the course of this work we have succeeded in gathering records of 1011 pairs of twins; either one or both twins in each pair have been afflicted with some mental disorder. In this material are included 234 pairs of twins with mental deficiency.

Our interest has been mainly in the so-called constitutional mental disorders. It could not be assumed that the relative importance of hereditary and environmental factors was the same for all clinical groups, or even for all cases in any one clinical group. As regards the mental deficiency group our first assumption was that in connection with it the hereditary factors were more important than in any other group among the constitutional mental disorders.

However, as the material accumulated, it became increasingly evident that the mental deficiency group was one of the most heterogeneous and at the same time, perhaps, the least hereditary one among all those included in our study.

As we scrutinized our material it appeared more and more definitely that the simple division of factors of human situations into those of heredity and environment was misleading in that it tended to draw attention away from complexities which should receive detailed consideration.

In the literature pertaining to the causation of mental disorders one finds reference to factors designated not only as hereditary, but also as inborn, congenital, pre-natal, constitutional, and the like. We believe that with the aid of properly selected material a more exact terminology and a more complete classification of etiologic factors can be devised.

While such material as ours cannot give us any idea of the *nature* of etiologic factors, it can indicate quite definitely the *developmental period in which such factors are operative.*

To be more specific, etiologic factors can be classified as follows: pre-germinal, germinal, embryonic, fœtal, natal, and as of various periods of post-natal development.[1]

The factors which we would designate as *pre-germinal* are the only ones which may properly be spoken of as hereditary. They are the factors which are already operative in the ancestry of a given generation before that generation has entered upon the very beginnings of its existence in the form of primordial follicles in the ovary and of spermatocytes in the testis.

To establish the influence of a pre-germinal factor in the etiology of a given mental disorder it is not enough to show that it runs in families; that fact alone can often be accounted for by the exposure of various members of the given familial groups to the same conditions. But if, in addition to the familial occurrence of a given disorder, it may be shown that such disorder, if found in one of a pair of monozygotic twins, regularly affects the other as well; and if it may be shown further that if such disorder is found in one of a pair of dizygotic twins, the other twin is, in most cases, free from it; then we have an accumulation of evidence sufficient to establish a pre-germinal factor as the sole or principal factor in the causation of the disorder under consideration.

Germinal factors in the etiology of mental disorders have received inadequate attention, and when referred to at all have often not been distinguished from pre-germinal factors.

The germinal period of development is a long and highly complicated one. There is evidence in the data of human histology that all the primordial follicles out of which ova are eventually to develop exist in the ovary of the female infant at birth, and, in fact, for several months before birth. It will be seen, then, that before an ovum has matured and become fertilized by a sperma-

tozoon, it has been in existence for a period of from 12 to 40 years—more or less—during which time it has gone through various phases of development. During this period it has been exposed to factors which have either fostered or hindered its development or which have, perhaps, had a disease-producing effect.

The germinal history of a spermatozoon, while quite different from that of an ovum, nevertheless also occupies a considerable period during which it may be exposed to various factors for better or for worse.

There are some abnormal conditions which do not seem to run in families and are, therefore, not strictly hereditary, but which can, nevertheless, be shown to be caused by germinal factors. A striking instance in point is that of mongolism. Among monozygotic twins, if one is a mongol, the other is quite invariably also a mongol. Among dizygotic twins, it is quite regularly observed that if one is a mongol, the other is normal.[2]

Mongolism is scarcely ever found in more than one member of a familial strain. Moreover, mongols are sterile and short-lived, so that direct inheritance is practically out of the question.

There is reason for thinking that sclerotic and atrophic changes in the ovary can so injure an ovum during the germinal period as to produce mongolism.

The *embryonic* period of development extends from the time of fertilization of the ovum to the end of the eighth week of gestation. During that period tissues and organs develop, and the architecture of the body is laid down. Pathogenic factors which are operative in that period are apt to produce conditions which are associated with malformation or monstrosity. A condition of this kind, if found with relative frequency in only one of a pair of monozygotic twins, may be definitely attributed to an embryonic factor and not to an hereditary or germinal one; although it would be, of course, inborn or congenital.

The *fœtal* period begins at about the end of the eighth week of gestation and terminates at birth. It is a period mainly of growth in size and not so much one of tissue and organ formation as is the preceding period. It is also a period during which the functions of nutrition, respiration and elimination are vicariously performed for the fœtus by the mother through the medium of the placental circulation.

Nutritional, circulatory, or renal inadequacy in the mother, systemic infections, certain pelvic conditions, and infarctions of the placenta are among the disease-producing factors which may be operative in the fœtal period.

Etiologic factors which are operative in the fœtal period may be known by their tendency to bring about the same or similar conditions in both of a pair of dizygotic twins with a frequency greater than among pairs of siblings. This, then, constitutes a criterion for separating out another group of inborn or congenital or constitutional conditions, attributable, however, not to pre-germinal, germinal, or embryonic factors, but to factors operative in the fœtal period of development.

We shall not enter here upon a discussion of disease-producing factors operative in the *natal* and various *post-natal* periods, as they are, for the most part, well known, although it is not always clearly recognized that a so-called constitutional mental disorder may be produced by such factors, and that there is nothing whatever hereditary or even inborn in the causation of such disorders. Ontogeny is not completed at birth and arrests of development may occur at any time before maturity is attained.

With reference to the above-described classification of constitutional factors of mental disorders, it may further be noted that it is possible to distinguish three types of etiologic mechanism. These may be designated as simple, multiple or variable, and complex.

We use the expression *simple etiology* in those cases in which the disease-producing action of a factor is limited strictly to only one of the developmental periods already enumerated. As an example of such a case may be mentioned Huntington's chorea, which is produced by a pre-germinal factor and nothing else. As another example may be mentioned mongolism, already referred to, as a condition caused solely by a germinal factor.

We speak of *a multiple or variable type of etiology* in connection with conditions which may be produced now by a factor operative in one period of development and now by a factor operative in another. Perhaps the most outstanding example of such a group of conditions is that of mental deficiency.

There is ample evidence, including some contained in our own material, that a great deal of mental deficiency is produced by an he-

reditary (*i. e.,* pre-germinal) factor. There is, however, equally strong evidence that it may be produced also by factors which are operative in any of the other developmental periods.

It is the principal object of this communication to present some newly gathered material having a direct bearing on the question of etiologic factors of mental deficiency which are operative in the fœtal period of development.

It is also well known that a considerable percentage of cases of mental deficiency is caused by head injury at birth [3] and by post-natal factors, such as meningitis or encephalitis occurring in infancy.[4, 5]

We speak of *complex etiology* in connection with those cases in which two or more factors operative in different developmental periods are required to produce the condition in question. This has been recognized in medical discussions in which both predisposing and precipitating causes have been stressed.

Examples of complex etiology are also to be found in the mental deficiency group. We would refer particularly to certain cases of Little's disease. Under the influence of some etiologic factor operative in the fœtal period of development, a child is born prematurely and in a markedly under-weight condition. Many such premature children eventually attain full physical and mental development. It is well known, however, that immature fœtuses are particularly liable to suffer intracranial hemorrhages during the birth process by reason of the vulnerable condition of the not-fully-developed blood vessels. In cases in which more or less extensive cerebral injury has resulted from such a hemorrhage, the child may be found to have Little's disease together with mental deficiency. In other words, a predisposing factor operative in the fœtal period and causing premature birth, plus a precipitating factor operative in the natal period and causing cerebral injury, have together resulted in mental deficiency associated with spastic paralysis. Presumably, in such cases the relative prominence of the neurologic syndrome and of the intellectual defect is determined by the localization of the cerebral damage. Some cases may be characterized by marked mental deficiency with almost complete freedom from neurologic disability; others may be characterized by marked spastic paralysis without demonstrable defect of intelligence; while in the majority of such cases both physical and mental handicaps are to be observed.

II. Intelligence in Twins.

That intellectual endowment—high, mediocre, or low—is determined in the first place by pre-germinal, *i. e.*, strictly hereditary, factors is indicated by measurements of intelligence in groups of persons representing different degrees of genetic relationship. An excellent summary of studies of this type is presented in the following table, copied from Sandiford,[6] giving coefficients of correlation in intelligence for certain specified groups.

Group.	r
Physically identical twins	0.90
Like-sex twins	0.82
Fraternal twins	0.70
Unlike-sex twins	0.59
Siblings	0.50
Parent-child	0.30
Cousins	0.27
Grandparent-grandchild	0.15
Unrelated children	0.00
Orphans	0.00

Among the conclusions drawn by Sandiford is the following:

The amount of resemblance in general intelligence varies from $r = 0$ for unrelated individuals to a maximum of $r = 0.90$ for physically identical twins. Intermediate values are found in accordance with the genetic relationship of the individuals. Therefore, there is an increasing degree of resemblance in general intelligence among human beings with an increasing degree of blood relationship among them. *Ergo*, general intelligence is an inherited trait.

The pre-germinal or hereditary origin of intellectual endowment is further indicated not only by family studies such as those of Galton,[7] Terman,[8] Goddard,[9] and many others, but also by the results of intelligence tests applied to twins.

In connection with our study of mental disorders in twins, we have gathered for use as control material records of intelligence tests made in normal twins—*i. e.*, twins free from mental deficiency or other mental disorders—among children in the schools of Los Angeles and neighboring towns.

In this material are included 148 pairs of twins with superior intelligence. One or both of the twins in each pair have an I. Q. of 120 or over. These cases are classified as follows:

	Pairs.
Monozygotic, male	15
Monozygotic, female	19
Same-sex, dizygotic, male	19
Same-sex, dizygotic, female	22
Opposite-sex, dizygotic	73

In all but four of the 15 pairs of monozygotic male twins, and in all but five of the 19 pairs of monozygotic female twins, the I. Q.'s of the two twins were either equal or differed by not more than five points.

That is to say, in about three-fourths of all the cases of monozygotic twins the intelligence score was either exactly the same for the two twins or showed a difference well within the limits of technical error. In the remaining cases there were differences in I. Q. points distributed as follows: 6, 6, 6, 7, 8, 13, 14, 15, 32.

In so far as these differences are in excess of technical error—surely in the last four cases—the contrasts cannot be due to pre-germinal or germinal factors (*i. e.*, to differences in original endowment), but must be attributed to factors operative in later periods of development—embryonic, fœtal, natal, or post-natal.

The corresponding figures for the dizygotic twins make a very different showing. In but four of the 19 pairs of the same-sex, dizygotic, male twins; in three of the 22 pairs of the same-sex, dizygotic female twins; and in twelve of the 73 pairs of opposite-sex twins were the I. Q.'s either the same or differing by not more than five points. That is to say, the intelligence of the two twins was the same in only one-sixth of the cases, as contrasted with three-fourths in the preceding group. The remaining five-sixths of the cases showed differences in I. Q. of from 6 to 53 points, distributed as follows:

6- 9 points	in 13 cases.
10-19 points	in 35 cases.
20-29 points	in 29 cases.
30-39 points	in 10 cases.
40-49 points	in 7 cases.
53 points	in 1 case.

These differences are, of course, for the most part, if not entirely, differences in original endowment.

Turning now to our records of twins with mental deficiency, totaling, as already stated, 234 pairs, our observation yields the same general result. These cases are classified as follows:

	Pairs.
Monozygotic, male	43
Monozygotic, female	44
Same-sex, dizygotic, male	28
Same-sex, dizygotic, female	38
Opposite-sex, dizygotic	81

In all but two of the 43 pairs of monozygotic male twins, and in all but five of the 44 pairs of the monozygotic female twins, both twins in each pair had mental deficiency; the I. Q.'s were the same in the two twins of each pair or differed by not more than five points in 51 cases; they differed by more than five points in 23 cases; and the I. Q.'s were not given in 13 cases. The range of differences in I. Q. was from 6 to 49 points in the 23 cases.

The corresponding figures for the dizygotic twins are as follows: in 19 of the 28 male cases; in 18 of the 38 female cases; and in 34 of the 81 cases of opposite-sex twins only one twin in each pair had mental deficiency, the other being of normal or superior intelligence. In the entire group of 147 pairs of dizygotic twins the I. Q.'s were the same in the two twins or differed by not more than five points in but 27 cases; they differed by more than five points in 86 cases; and they were not given in 34 cases. The range of differences in I. Q. in the 86 cases was from 6 to 69 points.

The data revealed by this material are in perfect harmony with the theory that *strictly hereditary (pre-germinal) factors determine only the maximal intellectual development that a given individual may attain;* that a certain unknown proportion of cases of mental deficiency are of hereditary etiology; and that factors operative in the pre-natal, natal, or post-natal periods may impair the inherited endowment either slightly, *i. e.,* bringing it down to a mediocre but still normal level, or markedly, *i. e.,* bringing it down to the pathological and disabling level of mental deficiency.

This state of affairs would seem to afford an explanation for differences in mental function which have been observed in Siamese twins [10] who, surely, have not only the same heredity but also are exposed to the same post-natal environment.

Possible happenings in the fœtal or natal period would suggest also a new interpretation of the findings revealed by mental tests applied to so-called identical twins reared apart.[11] In the light of such possible happenings it could hardly be taken for granted that any differences between the twins in such cases are necessarily to be attributed to differences in their post-natal environments. When a large amount of such material has been gathered, then—and not until then—shall we have an opportunity of comparing it statistically with cases of so-called identical twins reared together and noting whether those reared apart differ from each other more often or more markedly than those reared together.

In view of what has been said, a closer investigation of etiologic factors of mental deficiency which may be operative in the fœtal and natal periods of development would seem desirable.

In the early stages of our investigation it became quickly apparent that among inmates of institutions for the feeble-minded there was a much higher proportion of twins than among psychotic patients in state hospitals or among prison or reformatory inmates.

Other students have reported similar observations. To take an example from the recent literature, Carl Looft states: "By statistical data I have shown that there are more twins among imbeciles and the feeble-minded than among normal children. By an examination of a group of 64 pairs of twins I have also shown that the number of imbecile and feeble-minded subjects among them is greater than among children who are not twins." [12]

Disease-producing factors operative in the fœtal period of development are well known to be capable of causing death of the fœtus with resulting still-birth, or premature birth, or the birth at full term of a markedly under-weight child. These premature and under-weight children have a much higher mortality than children born at full term and of normal weight, scarcely 50 per cent of them surviving the first year of infancy.[13] These hazards of pre-natal life are much greater for twin than for single pregnancies, as is constantly revealed by obstetrical experience.[14, 15] Our material seems to indicate that the hazards are not only those of premature birth, physical under-development, and high mortality in the first year of infancy, but also of serious interference with the development of intelligence.

The pre-natal handicaps of twin pregnancy may affect both twins equally; or they may affect them both, but unequally; or they may affect only one, and the other not at all; and it is by no means inevitable that either twin be affected at all. It is merely that twins are more likely to be affected by such handicaps than children born singly.

A crucial test of this matter may be accomplished by a comparison of groups of twins with groups of siblings with mental deficiency, as has been done by D. G. Humm.[16]

Monozygotic twins cannot be employed for the purpose of such a comparison, as they represent a degree of genetic relationship which is much closer than that of siblings, having presumably an

identical hereditary endowment. But there is no reason for supposing that between dizygotic twins there is a closer genetic relationship than between siblings. In so far as mental deficiency is of hereditary etiology, it should not be more common among the dizygotic twin brothers and sisters of affected individuals than among their siblings. If found to be more common it could be attributed only to pre-natal or natal factors which are more often at work in twin than in single pregnancies.

Among our 147 pairs of dizygotic twins, selected by reason of at least one of the twins in each pair having mental deficiency, we find that the other twin also had mental deficiency in 71 cases (48.3 per cent).

Among the 182 brothers and sisters (not twins) of his 50 selected subjects with mental deficiency, Humm found that only 24 (13.2 per cent) also had mental deficiency.

In his paper Humm has compared only opposite-sex twins with opposite-sex siblings in order to avoid the possible error of mistaking monozygotic for same-sex dizygotic twins. However, the results revealed by his comparison are essentially the same as the above; and we find ourselves in full agreement with his conclusion in this connection, which is as follows: "It appears that some prenatal factor or factors other than heredity also enter into the causation of mental deficiency and that such factor or factors operate more frequently in the cases of twins than of siblings."

III. Brief Review of Literature.

The literature pertaining to the subject of premature birth and under-weight condition at birth deals quite fully with the physical phases of it, but rather inadequately and inconclusively with the mental phases.

The preliminary step in connection with such researches must be, of course, to determine when a birth is to be counted as a premature one and what weight at birth is to be counted as significantly under normal. Any line of demarcation that may be drawn between full-term and premature birth and between full-weight and under-weight condition at birth must necessarily be at a more or less arbitrary point. Such point is chosen in a manner judged to reveal in a most reliable way the pathogenic effects of prematurity and

under-weight condition in a mass of material subjected to statistical treatment by application of uniform, though arbitrarily selected, standards of normality.

A birth at full term, according to the standard generally accepted among obstetricians, is one which occurs at the expiration of 280 days from the beginning date of the last menstrual period. There is, however, a great deal of variation in both directions as to the length of this period. Thus, according to the often-cited statistics furnished by Zangemeister,[17] the duration of this period in a series of 3005 births was distributed as follows:

150-260 days..... 351 cases.
261-300 days..... 2359 cases.
301-370 days..... 295 cases.

As regards weight at birth, too, there is a wide range of variation found within normal limits. The distribution of weights in Zangemeister's 3005 cases was as follows:

2000-2499 grams..... 148 cases.
2500-3999 grams..... 2699 cases.
4000-5750 grams..... 158 cases.

There is, of course, an obvious correlation between duration of the period of gestation and weight at birth; but it is not a complete correlation. It is possible for a pregnancy to proceed far beyond normal term and yet result in the delivery of a markedly under-weight, immature fœtus; and it is equally possible for a birth to occur at the end of but 260 days or less from the date of onset of the last menstrual period and yet result in the delivery of a distinctly over-weight fœtus, as is shown in the following table, compiled from Zangemeister's figures:

Duration of pregnancy (in days elapsed from onset of last menstrual period).	Weight at birth in grams.					
	2000-2499		2500-3999		4000-5750	
	No.	%	No.	%	No.	%
150-260	63	17.9	277	78.9	11	3.1
261-300	75	3.2	2160	91.6	124	5.2
301-370	10	3.4	262	88.8	23	7.8

Arvo Ylppö,[18] who has been a leader in this field of research, is of the opinion that *immaturity,* as indicated by under-weight condition, is of greater moment in this connection than *prematurity,* as judged from the duration of the pregnancy. Accordingly, he

and others following him have endeavored to simplify the problem by merely distinguishing infants weighing less than 2500 grams at birth from those weighing 2500 grams or more, regardless of the question of premature birth or birth at full term or beyond normal term.

In our study we have taken cognizance of either premature birth (three weeks or more before term), or underweight condition at birth (5½ lbs., i.e., 2494.8 grams, or less), or both.

The *causes* of premature birth or of under-weight condition at birth are unknown for over 50 per cent of the cases. In some cases there seems to be a familial or an habitual tendency toward premature termination of pregnancy. It is distinctly more common in primiparæ than in multiparæ. *The hazard of premature birth, or of under-weight condition at birth, or both, is at least 10 times as great in multiple as in single pregnancies.*

Among the ascertained causes of prematurity are to be mentioned, in the first place, general diseases in the mother, including those which constitute indications for artificial induction of premature labor: syphilis (in about three or four per cent of all cases), tuberculosis, acute infections, general malnutrition, anæmia, heart disease, nephritis, eclampsia, etc.

Another group of causes consists of local conditions in the mother, such as narrow pelvis, uterine displacements, pelvic tumors, pelvic infections, and the like. Trauma or undue physical strain should, perhaps, be included here.

Finally are to be listed pathologic conditions of the placenta, including placenta prævia, twists or kinks in the umbilical cord, hydramnios, and diseases of the fœtus.

The relative importance of these groups of causes is approximately in the order of their listing here. Detailed statistics are to be found in the publications of Ylppö (*loc. cit.*), Capper,[19] and others.

Obstetrical statistics invariably show that there is a much higher *mortality* in infancy and early childhood among premature children than among those born at full term. In the series of cases reported by Ylppö the deaths occurred in the following percentages: by the end of the first day 9.28 per cent; by the fifth day 17.96 per cent; by the end of the first month 30.84 per cent; by the end of the sixth month 41.17 per cent. Further follow-up investigations

(omitting 70 cases which could no longer be traced, out of a total of 668 cases in his series) showed that by the end of the first year 50.33 per cent of the children had died; by the end of the second year 52.67 per cent; by the end of the third year 53.34 per cent; and by the end of the fourth year 53.51 per cent.

There is a definite correlation between the infant mortality rate and the degree of under-weight condition at birth, as shown by the following figures also reported by Ylppö. The percentages of children who had died by the end of the first year were as follows, classified by weight at birth:

600-1000 grams	94.4 per cent.
1001-1500 grams	65.1 per cent.
1501-2000 grams	44.9 per cent.
2001-2500 grams	33.5 per cent.

Data revealed by autopsies upon such cases indicate that the most important factor underlying the *pathology* is a vulnerable condition of the blood vessels due to their immature state of development. One finds quite uniformly more or less extensive hemorrhages into the skin, muscles, lungs, pericardium, gastro-intestinal canal, liver, kidneys, peritoneum, cranial cavity, spinal canal, and elsewhere.

The intracranial hemorrhages are among the most common, seem most frequently to be the immediate cause of death in the neonatal period, and are, no doubt, to be held responsible for the bulk of mental deficiency to be observed among the patients who survive.

Such hemorrhages are the result of birth trauma to which premature babies are much more liable than those born at full term. They are more common and more severe in breech than in head presentations.

The hemorrhages may be massive and, as regards localization, subdural, subarachnoid and intrapial, intraventricular, or into the cerebral substance; or they may be punctate in type, more or less widely scattered but often scarcely visible to the naked eye and associated with "softening," *i. e.*, beginning necrosis of nervous tissue.

These evidences of cerebral damage have been observed by Ylppö,[20] Capper and others, but their most thorough investigation seems to have been accomplished by Philipp Schwartz,[21] who has succeeded in tracing their relationship to certain neurologic and psychiatric conditions observed in later life.

Schwartz's study was of the pathologic anatomy of affections of the central nervous system following head injuries at birth. Cases connected with full-term as well as premature birth were studied. An essential feature of his technic was the routine practice of fixation of the entire brain in formaldehyde preliminary to its gross and histologic examination.

It seems that such lesions as " porencephaly," " diffuse sclerosis," " lobar sclerosis," " congenital cerebellar atrophy," and the like are but the end results of birth traumas. Schwartz believes that his findings suggest a promising direction for the investigation of " inborn " defect conditions, especially epilepsy, idiocy, and Little's disease.

As to the frequency of these traumas, Schwartz states that they constitute the dominant feature of the pathology of early infancy. In two-thirds of all autopsies performed upon still-born babies and upon those dying within the first five months of life, such hemorrhages and softenings of the brain were found. Undoubtedly the proportion is much higher in premature than in full-term babies.

Among the surviving premature babies are to be observed more or less frequently clinical evidences of brain injury, some of which seem to be fully recovered from eventually, but others remaining as permanent residuals.

Premature babies also present other peculiarities which distinguish them, as a group, for a time from full-term babies: almost regularly and early appearing *rickets*, presumably due to inadequacy of the mechanism for mineral metabolism in the immature organism; *anæmia*, presumably attributable to immaturity of the hamatopoietic system; umbilical or inguinal *hernia; spasmophilia;* and generally *retarded growth* in stature, weight, chest circumference, etc.[22] All these manifestations are for the most part transitory and are finally outgrown and overcome by the age of five or six years in almost all cases.

Among the " nervous " disturbances observed as residuals of birth trauma with special frequency in premature children Capper mentions not only Little's disease and epilepsy, but also enuresis, deaf-mutism, night-walking, nervous digestive disturbances, muscular hypertonicity, increased patellar reflexes, etc.

As regards mental residuals in the shape of either definite mental deficiency or intellectual backwardness within normal limits, there

seems to be no full agreement among the students of premature children. The data that have thus far been made available seem not quite conclusive.

Ylppö has made a follow-up investigation of 668 premature and under-weight children for periods up to the age of 8 years in some cases, but in most cases not beyond pre-school ages. Not counting the children who had died or who were lost track of, he found in 7.4 per cent idiocy or definite imbecility and in 3.1 per cent Little's disease. This did not include borderline cases "concerning which in young children one could not say whether the condition is not merely one of temporary retardation of mental development with good prognosis." No mental measurements are reported by him.

Maria Comberg [28] reports results of a follow-up investigation of 97 surviving premature children. Of these 8 had died in early childhood, subsequent to their first observation in the hospital in the neo-natal period; 16 were lost track of; 2 were reported by a hospital interne to have shown evidences of Little's disease, one of these without complicating mental deficiency; 2 gave the impression of being slightly feeble-minded, although the author considers this judgment as subject to doubt in these cases; and only 1 was definitely an idiot—possibly not related to premature birth, but rather to an obscure illness with cerebral manifestations occurring at the age of four months. The author's conclusion is to the effect that her material failed to support the contention that mental inferiority occurred as a result of prematurity either on a basis of cerebral hemorrhage or that of damage caused by rickets. However, a total of 6.8 per cent of cases of mental deficiency (including Little's disease and "slight" feeble-mindedness) is distinctly higher than is to be found in the unselected population.

In contrast with Comberg's findings are those reported by Capper: "Of 51 immature children of school age that presented themselves for re-examination, four had Little's disease associated with idiocy or imbecility; one was an idiot, and one child was of age but too small to attend school. Of the remaining 45 children, 15, or only one-third, were in classes that properly corresponded to their ages. Twelve children, or about 27 per cent, were one year behind their class, nine, or 20 per cent, were two years behind, two were three years behind and two were four years behind their class in school. Five children, or over 11 per cent, were attending schools

for mentally inferior children. Of the 15 that were not behind in their school work, only one was farther ahead in his school work than his schoolmates; all the others were average pupils and students." Mental measurements are not reported.

Capper's series of cases seems to contain a higher proportion of cases with mental deficiency and with neurologic disorders than other students of premature children have found in similar material.

Carl Looft [24] reports interesting observations upon six variously selected groups of cases.

The first group consisted of 38 premature children examined between the ages of 3 and 38 months. About three-fourths of these showed retarded development of intelligence; one had Little's disease. As is the general rule in such cases, all showed signs of rickets. Looft justly remarks:

> This retardation, like that of the growth of the body, stature, is transitory if there has not been a cerebral hemorrhage during birth. After two to four years most of these subjects will have attained a normal development; I have seen that many times. That is why such children should be examined at the age of four years or later.

Looft's second group of cases consisted, to begin with, of the babies that had been born in the maternity service of the city of Bergen, Norway, between the years 1910 and 1916, and weighing 2500 grams or under at birth. Excluding out-of-town children and twins (which were reserved for special study) there remained 91 children, 43 boys and 48 girls, all of school age. As psychiatrist for the Bergen city schools the author was able to examine those who were in the schools. Seven children were found to be retarded in school progress and were shown by intelligence tests to have I. Q.'s varying from 57 to 87. While this constitutes 7.7 per cent of the 91 cases, Looft states: "Assuredly this figure would have been greater if I could have known the future of all these 91 children after their discharge from the maternity service"; perhaps one-third or one-half of them had died.

Looft's third group of cases consisted of 532 backward children in the public schools of Bergen. Among these he found 29 cases—5.5 per cent—in which "the cause of the disorder of intelligence could only be the premature birth." Tests in these cases revealed I. Q.'s ranging from 43 to 88.

The fourth group consisted of cases seen over a period of 10 years in his private practice. There were 105 cases with a history of pre-

mature birth. Among these were found 10 cases (9.5 per cent) of disorder of intelligence, 19 cases (18.1 per cent) of Little's disease with disorder of intelligence, and 3 cases (2.9 per cent) of epilepsy with disorder of intelligence..

The fifth and sixth groups of cases consisted of inmates of institutions for the feeble-minded among whom there was a history of premature birth in from 8 to 10 per cent of the cases with definite information on the point in question. Control figures for comparison with the general population are not given.

In a preliminary report of a more recent study made in this country by Mohr and Bartelme [25] the authors express disagreement with the views of such writers as Ylppö and Capper and are inclined to agree rather with Comberg, who did not find in prematurity an etiologic factor of mental deficiency.

These authors report the results of ratings in intelligence based on Gesell's developmental schedules and on Kuhlmann-Binet tests. The clinical material consists of 113 premature children varying in age from 8 months to 7 years at the time of the examination, with a mean chronological age of 2 years 9 months. These were compared with their siblings.

Among the authors' conclusions are the following:

A comparison of performances of 50 individual prematurely-born children with those of their 40 full-term siblings, on the basis of the relation of mental age to chronological age in each case, revealed no significant difference in the mental development of the two groups, if due allowance is made for the period of prematurity.

The prematurely-born children did not differ from full-term children in the time of the beginning of eruption of teeth, in onset of walking, in beginning of talking and in the learning of bladder control, if correction was made for the period of prematurity. The smaller prematurely-born children were consistently a little later in these developments, but again the difference was minimized if this correction was made.

Hemorrhage and other injury at birth result in consequences to prematurely-born children that do not differ from those clinically noted among the children born at full term. If they occur more frequently among the prematurely born, they constitute an extra hazard of prematurity.

IV. Presentation of New Material.

At this point we wish to call the reader's attention to the fact that most of the clinical material heretofore utilized in studies of

the effect of prematurity on development of intelligence has consisted of premature children in the ages of infancy and the pre-school period. Obviously, this is not the material of first choice for the purpose in hand. In many cases, retarded development is observed at these ages which is but a transitory phenomenon and not one of established mental deficiency. Accurate mental measurements are not so readily made at these ages. Mental deficiency, especially in the higher grades, is not so readily detected in infancy and in pre-school ages as in elementary school ages, and its existence in very young children may often be overlooked.

Accordingly, material of first choice for the purpose of such a study would consist of children of elementary school ages.

We wish to call the reader's attention also to the fact that, in connection with most of the statistics pertaining to the incidence of mental deficiency among premature children, control figures from full-term children or from the unselected population are not furnished for comparison.

We shall now present our own material which has been specially gathered for this study.

The first question which was raised in our study was, *How does the incidence of premature birth (three or more weeks before term) and of under-weight condition at birth (5½ lbs. or under) among the feeble-minded compare with that in the unselected population?*

We obtained, partly from the institutional records and partly from the parents, the data concerning premature or full-term birth and weight at birth for a series of cases among the inmates of Pacific Colony (state institution for the feeble-minded at Spadra, California). The cases were taken in alphabetical order without selection, except that cases of mongolism were not included.

Not counting those cases in which the necessary data could not be ascertained (67 cases), we found ourselves in possession of data pertaining to 122 institutional cases of mental deficiency, distributed as follows:

	Cases.
Born at full term, weight at birth over 5½ lbs	96
Prematurely born, weight at birth not given	9
Born at full term, weight at birth not over 5½ lbs	9
Prematurely born, weight at birth not over 5½ lbs	6
Birth unascertained as to prematurity or full term, weight 5½ lbs., or under	2

Our control material was obtained by first going over the clinical records of all births in several hospitals in Los Angeles and in Pasadena, as follows: Pasadena Hospital for the years 1917-1926; Good Samaritan Hospital, 1922-1925; Hollywood Hospital, 1924-1925; White Memorial Hospital, 1924-1925; Los Angeles County General Hospital, 1925.

Altogether, 11,666 records were gone over for data concerning premature or full-term birth and weight at birth. Of this number only 9782 cases were used in our study, 1884 cases being eliminated, as follows:

	Cases.
Still-born	215
Died before leaving hospital	239
Multiple births (persons)	215
Data unascertained	1215

Among these 9782 cases we found 381 of either premature birth, under-weight condition at birth, or both, distributed as follows:

	Cases.
Born three weeks or more before term, weight over 5½ lbs.	23
Born three weeks or more before term, weight at birth not ascertained	11
Born three weeks or more before term, weight 5½ lbs. or under	208
Birth unascertained as to prematurity or full term, weight 5½ lbs. or under	26
Birth at full term, weight 5½ lbs. or under	113

It appears, then, that in our group of mental deficiency cases there were premature birth, or under-weight condition, or both, in 21.31 per cent; whereas in our control series obtained from maternity services the corresponding percentage was 3.89—somewhat under one-fifth as high.

Obviously significant as this contrast is, it is virtually certain that it greatly understates the case. We have already referred, in the preceding section of this communication, to the abnormally high mortality which occurs among premature children—amounting to 53.51 per cent by the end of the fourth year, according to Ylppö. It may be estimated that in an unselected group of children surviving to elementary school ages the percentage of cases of premature birth, or under-weight condition at birth, or both, would amount to about 2.5 in a random sampling of the population of Southern California under present conditions.

Accordingly, it may be judged that the incidence of premature birth, or of under-weight condition at birth, or both, is about eight times as great among institutional cases of mental deficiency as in the unselected population.

The second question which was raised in connection with our study was, *How does the incidence of mental deficiency among those of premature birth (three weeks or more before term) or those of under-weight condition at birth (5½ lbs. or under), or both, compare with its incidence in the unselected population?*

With that question in mind, we undertook a follow-up investigation of the 381 cases of premature birth or under-weight condition at birth to which we had found leads in the maternity records of the local hospitals, as detailed above. This investigation was made in the early part of 1933; therefore the ages of the children ranged between 6 and 16 years. We were able to find in the schools only 146 of the 381 children, the remainder having died, or moved away, or been otherwise lost track of.

The results of intelligence tests were available for almost all of these 146 children. The distribution of I. Q.'s among them is shown in the following table:

Under 56.	56-65.	66-75.	76-85.	86-95.	96-105.	106-115.	116-125.	126-135.	136-145.	Over 145.	Rated as "normal" or "superior"; I. Q. not ascertained.
3	2	10	10	24	31	33	19	5	2	1	6

If children with an I. Q. under 76 be counted as having mental deficiency, we find that in the group of cases under consideration the incidence of mental deficiency amounted to 10.27 per cent.

In Terman's [26] series of 905 unselected children of elementary school ages the percentage of cases with an I. Q. under 76 was but 2.63—about one-fourth of the figure for the premature and under-weight children.

Inasmuch as the more severe results of head injury at birth, such as idiocy and the lower grades of imbecility, also those cases of mental deficiency which are complicated with the crippling effects of Little's disease or with epilepsy, are automatically precluded from school attendance, it may be judged that here, too, the con-

trast between the premature or under-weight children and the control group, as revealed by our figures, is an understatement of the case—exactly to what extent, it would be impossible to say.

The evidence seems conclusive to the effect that premature birth or under-weight condition at birth is an etiologic factor in mental deficiency. For the most part, if not entirely, the damage in such cases is caused by cerebral trauma occurring during birth. Premature and under-weight children are much more liable to suffer such damage at birth than are children born at full term and of normal weight. Prematurity and under-weight condition at birth are much more common in multiple than in single births; for that reason, and probably by the same mechanism, mental deficiency is produced more often in twins than in single births.

It should be pointed out that our material demonstrates just as conclusively that premature birth, or under-weight condition at birth, or both, *per se*, do not cause mental deficiency. In our group of cases no fewer than 19.29 per cent of those in which the I. Q. had been ascertained showed an I. Q. of over 115. The corresponding figure for Terman's group of 905 unselected children is but 11.55 per cent. On this point our material bears out the contentions of such writers as Comberg, Mohr and Bartelme, and some few others.

V. Summary and Conclusions.

There is a great deal of evidence indicating that the large group of cases included in clinical classifications under the heading of mental deficiency is, from the standpoints of pathology and of etiology, a heterogeneous group.

Some cases are of simple etiology, by which we mean here that they are produced by a factor or factors operative in only one of the following developmental periods: pre-germinal, germinal, embryonic, fœtal, natal, and post-natal.

Other cases are of complex etiology, being produced by two or more factors operative in two or more of the above listed different developmental periods.

The main object of this communication is to present some newly gathered material demonstrating the production of mental deficiency by factors operative in the fœtal or in the natal developmental period, or, by complex etiology, in both.

We were led to undertake this study by some findings revealed by previously collected, as yet unpublished, material in our possession, consisting of records of 148 pairs of twins with superior intelligence and 234 pairs of twins with mental deficiency.

These findings consisted principally in (*a*) cases of markedly unequal intellectual development in monozygotic twins, and (*b*) evidence of greater incidence of mental deficiency among monozygotic and dizygotic twins than among single births.

A comparison of a group of twins with a group of siblings with mental deficiency indicated the existence of some factor or factors, operative in the fœtal or the natal period of development, or in both, and more often among twins than among single births.

A brief review of the more important contributions to the literature of this subject is offered. This deals with the causes of premature birth and of under-weight condition at birth; the mortality of premature infants; the findings at autopsies; and the general physical, neurologic, and mental peculiarities of surviving premature and under-weight children. As to the part played by premature birth or under-weight condition at birth in the etiology of mental deficiency, the material heretofore presented in the literature seems inconclusive.

The new material, gathered by us especially for this study, reveals that among 122 institutional cases of mental deficiency there were 26, or 21.31 per cent, in which there was premature birth (three weeks or more before term), or under-weight condition at birth (5½ lbs. or under), or both.

In a control group, consisting of 9782 births which occurred in five general hospitals in Los Angeles and Pasadena, the corresponding percentage was but 3.89. This figure is judged to be too high as there was no way of making proper allowance for the abnormally high mortality of premature children during infancy and pre-school ages. It is estimated that the incidence of prematurity and of underweight condition at birth among institutional cases of mental deficiency is no less than eight times as great as it is in the unselected population.

Our new material reveals, further, that among 146 children of elementary school ages, who had been born prematurely or were in under-weight condition at birth, there were 15 cases (10.27 per

cent) of mental deficiency (I. Q. under 76), *i. e.*, relatively nearly four times as many as the 2.63 per cent found in Terman's series of 905 unselected children.

This contrast, significant as it stands, is also probably an understatement of the case. Our follow-up investigations were conducted in the schools and therefore did not include the cases with the more severe results of head injury at birth, such as idiocy and the lower grades of imbecility, also those cases of mental deficiency which are complicated with the crippling effects of Little's disease or with epilepsy, all such cases being automatically precluded from school attendance.

The evidence seems conclusive to the effect that premature birth or under-weight condition at birth is an etiologic factor in mental deficiency. For the most part, if not entirely, the damage is caused by cerebral trauma occurring during birth. Premature and under-weight children are much more liable to suffer such damage at birth than are children born at full term and of normal weight. Prematurity and under-weight condition at birth are much more common in multiple than in single births; for that reason, and probably by the same mechanism, mental deficiency is produced more often in twins than in single births.

Premature birth, or under-weight condition at birth, or both, *per se*, do not cause mental deficiency. In our group of cases no fewer than 19.29 per cent of those in which the I. Q. had been ascertained showed an I. Q. of over 115. The corresponding figure for Terman's group of 905 unselected children is but 11.55 per cent.

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EXPERIMENTAL ANALYSIS OF THE PSYCHOPATHOLOGICAL EFFECTS OF INTOXICATING DRUGS.*

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Most of our knowledge of the influence that intoxicating drugs exert upon the behavior and experiences of human beings has been obtained through two main sources of information: (1) Studies made on persons who took drugs or were given them for the special purpose of producing certain effects. To this category belong the reports of both introspective and objective findings in persons who took the drugs for the gratification of cravings other than scientific, as well as reports of such effects where the drugs were administered for the purpose of experimental investigations. (2) Incidental observations made in cases where the drugs were administered primarily for the purpose of treatment.

The heterogeneous material that has come through the medium of the first of these two sources has gradually led to the appreciation of the close relationship that exists between these effects and phenomena observed in mentally diseased persons, suggesting this as a method for the experimental investigation of psychopathological phenomena. As was to be expected, these investigations attracted particularly those whose main interests lay in the study of mental diseases, so that the development of this work was closely linked with that of psychopathology, its succession of stages being directly related to the shifting of trends in psychiatry. Thus, we find that at a time when psychiatrists were mainly interested in the separation of descriptive symptom-complexes, the fact that some drugs could produce symptoms more or less similar to those found in certain disease entities was taken as the basis of the experimental approach. Kraepelin and Nissl, for instance, instituted their experiments with the hope that, in producing artificial psychoses through the effects of drugs on the one hand, and the histological

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examinations in cases of poisoning by these drugs on the other, they could determine the pathoanatomical substrata in certain mental diseases. With the progress in psychiatry and the appreciation of the more complex relationship existing between the personality of the individual and the symptoms observed, the center of attention shifted to more fundamental considerations, although the nature of these still remained on a descriptive basis. The reports of even some of the most recent investigations still show this adherence to an essentially phenomenological approach. Thus, the observations on the effects of mescaline (Beringer [1] and others) [18] center mainly about the changes produced in the functions of the special senses. The same is true of the experiments with hasheesh where interesting observations were made of changes in the perception of time and space. By the production in normal individuals of changes in the field of perception they hoped to gain insight into the nature of hallucinatory experiences. Another aspect of the same phase is found in the experiments undertaken on mentally diseased persons for the purpose of ascertaining the changes that may be produced in already established psychopathological experiences by the administration of drugs. These trends are especially well seen in the experiments of Kant [9] and those carried out by Zucker.[17] Kant, working with hasheesh, found that in patients suffering with certain mental diseases the psychopathological experiences were exaggerated by the administration of the drug. Zucker was particularly interested in comparing the phenomena induced by mescaline with those caused by the disease, and found that the hallucinations were essentially different from the pre-existing ones.

The appreciation that drugs could influence the behavior of human beings to such a pronounced degree, both in producing the above mentioned effects as well as the more general one of relief of pain, sedation, sleep, or stimulation, led to the numerous trials of drugs in the treatment of mental diseases. The observations obtained through this source, therefore, followed essentially the same trends as outlined above. The most important attempts in this direction were those of Berger [2] and his followers with cocaine, of Kläsi [10] with somnifen, and the use of sodium amytal by Lorenz and Bleckwenn.[8] Interesting as a discussion of the actual therapeutic value of these drugs may be, we wish to restrict ourselves here to the observations that were made of psychological phe-

nomena produced by these drugs. These were mainly confined to the changes in the emotional state and rapport of the patients, as well as to the greater or lesser ease with which they spoke of contents which they had previously covered up. In this field, too, then the interests remained, essentially, on a descriptive level. Within recent years, however, profound changes have taken place in psychopathological orientation. The attitude has shifted from a static to a dynamic evaluation, and from the minute observation of symptoms to the interrelationships between them and the total personality. Single symptoms or even symptom-complexes are not regarded as specific entities but as relative manifestations of deeper mechanisms. We have come to see that a given symptom may have different values in different patients, whereas apparently unrelated symptoms may express the same mechanisms under different settings. Furthermore, if we are to understand the symptoms properly, we need, besides a good description of the clinical picture, a detailed analysis of the personality as it was evolved through its development. If, then, we are to study the influences of the drugs on behavior and be able properly to evaluate them, we would have to change our attitude along the same directions. For this purpose we have undertaken the studies we wish to report on the basis of the following plan:

(1) The person to be investigated was to have been subjected to a thorough analysis of his development in relation to his environmental settings, so as to afford an insight into the meaning of the picture presented.

(2) Each of these persons was to be subjected to the effects of the same series of drugs which have been shown to have definite effects upon behavior. These drugs were to be administered under certain standard settings.

(3) Different persons showing different types of behavior were to be utilized for the experiments.

It was felt that in this way we could gain insight into the effects of the drugs used under conditions which would permit the separation of those effects that are characteristic of a certain drug from those that different drugs may produce in a certain personality or in a special syndrome.

Procedure.—The main experiments were carried out with six patients of this hospital: four schizophrenics and two psychoneurotics. A further series of observations was made on a number

of patients with regard to special phenomena and the effects of single drugs. In all of these patients the experiments were preceded by an analytic investigation of the development and experiences in relation to the problem presented. Four drugs were used: (1) Sodium amytal by intravenous administration in doses of 4½ to 7 grains. (2) Cocaine hydrochloride by subcutaneous injections in doses of 30-50 mg. in a 2% solution. (3) Hasheesh (American cannabis, Parke Davis Co.) in form of the extract in doses of 0.9 to 1.5 gm. (4) Mescaline sulphate (Merck & Company) by intramuscular injection in two doses of .2 gm. in distilled water with an hour's interval between the injections. Only short intervals of time were allowed to elapse between the administration of the different drugs to the same patient, so as to obviate the possibility of differences in the mental state of the patients. During the administration of the drug and following it the behavior of the patients and their productions were recorded in detail.

The following are summaries of our findings:

CASE I.—A. B., a 39-year-old, white American married woman. During the last five years she has developed lack of interest and ambition, ideas of misidentification, auditory and visual hallucinations, and neglect of her children. Her father died when she was nine years old. The mother is a quick tempered but kind woman who suffered for years with intense headaches. Patient is the youngest of the first husband's children. One half-brother was diagnosed dementia præcox. Her early development was uneventful. She married at twenty-seven a farmer who was not particularly attractive to her, and their marital life was not satisfactory. She taught school before her marriage and took a fairly active part in community life until her present illness. After the birth of her second child the patient seemed depressed and cried a great deal. She appeared preoccupied and sexually frigid. She began to insist that the child was not her own, that it belonged to her sister-in-law, who just brought it for the patient to take care of. She became irritable, at times over-talkative, began to talk to herself and express auditory hallucinations. During the last two years she became antagonistic against the oldest child, told him he was not her son, and developed suspicions against her husband, accusing him of sexual misconduct. During the last one-half year she entirely neglected her household and appeared absent-minded. She showed no insight into the change of her behavior.

On admission she was dreamy, complacent, playful, and misidentified members of the staff. She had visual and auditory hallucinations (such as the voices of school children whom she had previously taught). She had no insight, and her productions were fragmentary with occasional blocking. As much of the information concerning her background was obtained under the influence of the drug, we will report these in more detail.

EXPERIMENTS.

(1) She was given 7½ grains of sodium amytal intravenously. At first she was somewhat apprehensive, but relaxed immediately after the injection and began to talk to the physician in an intimate manner, as if she wanted to communicate things which she had previously withheld. She talked freely, without any blocking, and only occasionally made references to misidentification:

"At school I would play animal stories. . . . . It is more pleasant than real life. When I worked in the kitchen I would talk to kettles and pans. The hired man would make fun of me. . . . . Play life is better than real life, etc."

She continued in this manner, talking in a free and friendly fashion and bringing out a number of factors that could not be obtained from her before. The marital situation was unsatisfactory, probably on the basis of an early fixation on the father and a pronounced tendency to imagine herself as a boy. With this there was a great deal of day-dreaming and later on, even while she was teaching school, a lively imagination which made it easy for her in games, for instance, actually to identify herself with individuals or animals that she was personifying. In marital life she frequently took recourse to this when the situation became especially difficult. The last child was a disappointment because she had hoped it would be a girl and one that resembled her father. Soon after there were symptoms indicative of the menopause, and the patient, as she indicates, slipped into her world of fantasy.

(2) A few days after the sodium amytal the patient received 30 mg. of cocaine. Within ten minutes after the administration she became excited, her pulse rose to 140, and there was a marked tremor of her hands. She cried profusely and spoke rapidly in interrupted sentences. Most of the subsequent communications were uttered as if talking to herself without special reference to the examiner: Q. "Do you have any idea now why you came here?" A. "I don't know. When they let me out I thought I heard the kids bawling, so they put me back in again. I heard Basil yelling just now." Q. "Who am I today?" A. "I have been calling you Dr. ———, but I don't think you are. When I hear you I think you are Basil, then I am out to the country again." (Patient cries freely.)

The patient becomes more excited, crying and paying no attention to questions, but continuing to talk to herself in the same manner as above. The stream of her production is mainly centered about numerous sense deceptions she is having and which she accepts as real: She is being influenced by some one, she hears her son laughing, her hands are changed into man's hands, the right one being larger than the left. The right side of her body is scolding the left one, the right one being God and the left the Devil. She sees a black-haired girl's face in her genitalia and thinks she is pregnant again. The excitement continued all through the productions and lasted for about two hours. She then gradually became quiet and uncommunicative.

(3) A few days later the patient was given .4 gram of mescaline sulphate in two doses at 7.15 and 8.15 a. m. She became restless, throwing herself

from side to side, and appearing to be distressed by some experiences. When addressed by examiner she states: "They are trying to call all those nurses by name. I was out in the field. They were trying to see if I couldn't roll, roll, roll. It was so long. Ou! OU! Something is stinging my toes and fingers. You're pretty big this morning, and the girl looks little. Your hand is big too. You are so far away. I want to tell you about that where we were at. We were away down the hill. We were going to roll away down the hill. The nurses wouldn't let me. They said the lake was down there. I'd like to go swimming in the lake. I didn't have my bath this morning. That kind of roll was for my dinner. I see you sometimes in my eyes. Sometimes you look like a little girl floating around in the air. You're growing bigger." (Patient seems preoccupied and does not answer for several minutes.) Then she says: "Why do you go away and then come back again? Your hand is all shriveled up and don't look very good. Oh, it's bigger. One side grows bigger and the other side smaller . . . . I can see blood coming out of somebody's ear. I can't see who it is. It's coming out lots and lots. I see Daddy. No, it's you. Where in the dickens is it going again? Daddy has black hair, brown eyes. I want brown eyes but I got blue. (Sudden outburst of laughter.)

The patient continued in this manner in a rapid stream of talk. After a while, however, the intervals of self-absorption and silence became of longer duration, broken by sudden outbursts of giggling and occasional statements. After four hours in all, the patient finally became quiet and was silent for the rest of the day.

(4) The patient was given .9 gram of extract of cannabis indica. After about an hour she became restless, absorbed, and quite unwilling to talk. Questions were answered with statements, "I am thinking. Let me read a book. What do you want?" There was no sign of catatonic phenomena or peculiar attitudes. No evidence could be obtained of her hallucinatory experiences at this time.

In retrospect we have the following report: "You were too big. I was too little. Sometimes you looked awful big. I was listening to beautiful music. I woke up at Walter's place. This is not the same place. The furniture doesn't fit. There was electricity going on in the room. It still makes me go up and down. I heard both girls' and boys' voices. They were coming in from outdoors and laughing at me."

No further information could be obtained. She had no insight into the fact that her experience could be related to the medication and seemed not to notice any essential difference between these experiences and her usual ones.

CASE II.—R. N., a 23-year-old, white American male, admitted on March 4th because of irrational utterances and fearful, apprehensive behavior. He was an only child who grew up under the influences of an over-exacting father and a lenient mother who would alternate between protecting the boy against the father and asking him to take her side in disagreements with her husband. He developed into a quiet, earnest youth who talked little,

carried out his duties meticulously, and was well liked although he had few friends. At the age of twenty he made several attempts at contacts with girls of his social level but gave up after a few months because he felt other boys interfered. Two years ago a gradual personality change set in. He started to drink and have promiscuous relations with prostitutes. He became sullen, antagonistic against his father, and began to write checks on his father's name. In December, after a dramatic scene, his father asked him to leave the house. The patient went to work in a lunch room but was induced by his mother to return home six weeks later. On re-entering the home he seemed ill at ease and undecided what to do. The next day he was apprehensive, went to the church stating that he had to make a confession, and then went home where he told his father he had acquired a venereal infection. From then on he thought that some men were after him. He began to hear accusing voices and became less and less communicative.

On admission he showed stiffness and hypokinesis but no catalepsy. He was hallucinated, and at times became assaultive against the attendant who, he thought, gave him dirty food. There were no physical complications except for gonorrhea and arthritis in both feet. After the recovery from the phase of apprehensive withdrawal, the patient continued to be evasive, at times absorbed and at other times antagonistic, or silly and annoying to the other patients. It was impossible to get any information from him under the usual conditions. Whenever approached he would say that he was all right except for his feet and that he should go home.

Experiments.

(1) He was given 7½ gr. of sodium amytal. Following this he began to talk more freely, complaining of peculiar somatic sensations. "My teeth feel as if they are falling out. My bones feel as if they are gone. My chest is too narrow. I used to have a wide, deep chest, but it has been shrinking, etc."

Throughout the interview the patient remained friendly and jolly. He spoke about his experiences in the hospital. When asked why he was praying, while in seclusion, he answered, "I prayed just because it was an old custom with my mother." He also stated that the food given to him tasted as if something was in it which shouldn't be there. A lot of things were happening which he can't remember now. He had many dreams, felt mainly distressed about being locked up. The dreams were induced by "some fellows in the hallway who were trying to influence" him. They showed him pictures and made him angry. "I have an awful temper. They put into me ambitions to kill. I might have killed a lot of people. People seemed to look like figures in a theater. I wanted to take things in my own hands and do like I wanted to."

However, when asked the reasons for his coming here and his own personal experiences, particularly with reference to his sexual life, the patient remained uncommunicative and no pertinent facts could be obtained. After the effect of the sodium amytal had disappeared he continued as he had before the injection.

(2) Several days later he was given 50 mg. of cocaine. He became restless, often raising himself on the bed and wanting to move around. "I don't think there's anybody against me. It doesn't bother me any way." He admitted hearing voices but would not tell what they said. He became angry and antagonistic. "I will tell you what's bothering me. I came here as a state patient and didn't have any money. You fellows could do with me what you wanted. I would like to know how things stand with me. My body has changed considerable, and I have decided to go home now. There's a thing I can't explain. I just get angry. Maybe some day I will get after you." "Why did you speak so much about your mother at first?" "Well, a mother is a very dear thing. Somebody was talking behind my back. Nobody came up to me and said anything really to my face. When one is buried, that's all there is to it." He quieted down rather rapidly, ceased his demands to be released, and returned to the behavior which was present before the drug was given.

(3) Several days later the patient received .5 gm. of mescaline sulphate in two doses at an hour's interval. For the first two hours there were practically no communications. He remained quiet, complacent, somewhat absorbed, and reluctant to answer questions. No more illuminating statements could be obtained than the following: "I just feel kind of funny, light. At times your face looks broad and at times it looks narrow. Every time you come in here, my eyes get funny, wavering around. I guess you have a strange influence on me. My bones are drawn up and stretched out. There are lines running around my eyes. My hands are getting smaller. Things don't smell fresh."

(3) The following day the patient received .9 gm. of cannabis indica by mouth. He showed dilation of his pupils, increase of pulse rate to about 100, became quiet and mute except for occasional utterances—"yes and no." After two hours he stated: "I am just feeling kind of weak and numb. I am floating in the air. My eyes are fluttering. My legs are heavy. I don't seem to be able to keep my eyes open." After a long silence: "My parents have been swell, too much for me. Had an argument once. It was all my doing. Always had a high temper. In my life it feels like heat waves." At times he appeared suspicious, looking around in an alert fashion. At other times he dozed. At noontime he returned to his usual complacent and seclusive attitude.

CASE III.—M. K., a 25-year-old, white American girl admitted on December 16th. For eight months she had shown personality changes of a schizophrenic nature. Both parents were of schizoid makeup. The child was born a few weeks after her little brother had died, and the mother had expressed her disappointment about her being a girl. She grew up a dependent, sensitive, somewhat stubborn child with no warm contact with her father, but leaned towards her mother so much that she was called "mother's cry baby." Being of good intelligence, she had no school difficulties, but was unable to make friends, spending most of her time working and playing around the home with her mother. When she was fourteen a German cousin came to live with the family. The patient became attached to him, always wanting to be where he was, but hiding this from him and never showing any sexual

interest in him. The family did not approve of this and tried to separate them. It was finally decided to have the girl go to New York, where she did good stenographic work and lived with an aunt. While there she became interested in a Jewish artist, but broke up this relationship because of the aunt's objections to it. About ten months after this, however, she began to talk about being hypnotized by him. This led to her return to Iowa. When she reached home she began to express her regrets for having left the man. She lost interest in things, and the attemps of the family to arrange a friendship with a boy of the neighborhood were unsuccessful. There followed attempts at heterosexual relations which failed, and the patient became depressed and withdrew into herself. She was first admitted to the General Hospital. There she was depressed and preoccupied, and was placed on luminal. When seen in consultation a few days later, she cried a good deal, was apprehensive, unwilling to commit herself about any matters of her past, but reaching out for help. At subsequent interviews she began to express paranoid ideas, being afraid that the examiner was trying to influence her by mysterious means and was trying to get her away from her mother by making another woman appear like her mother. She was admitted here three months later in a state of excitement, calling loudly for her mother, refusing to eat, and not allowing any contact with her. She talked in a bizarre, fragmentary fashion: "Everything is going around and around. The nurses are changing places. They are slipping one into another. They are using a code system on me." The patient danced around at times for several hours, stating that in this way she could exchange places with the nurses. At times the patient stared into space, preoccupied. She refused to eat and resisted tube feeding. Physically she was of an asthenic build, showing no sign of disease except a mild anemia.

Experiments.

(1) Sodium amytal, 7½ gr. intravenously. She was quite resistive to the injection, but five minutes later, just as the injection was finished, she showed a marked change in facial expression. She became complacent and capable of talking freely in a matter of fact way. Physically she showed mydriasis, nystagmoid jerks of the eyes, and a speech defect. The productions were as follows: "Everything was twisted around, but I am all right now. The last couple of nights my mind went from the upper lip of my mouth and three times across the forehead. There was a girl friend of my mother's here, and I tried to tell her everything. The day I came to the hospital there was a physical change in me. I had the feeling of a girl who was going . . . . and then the feeling of a boy." Q. "What was the difference? Where was it?" A. "Well, I felt like a baby. I got the impression from the dreams I had before that I was supposed to be my mother's little boy. I thought that perhaps that was . . . . if I would have lain still and listened to my mother, I would have been a boy, but this way at times I am a girl and at times a boy . . . . . My mother had a little baby boy that died when he was five years old, and during the time that he came into the world I was born. When I was

born he was five. I don't know whether she wanted me to be a boy or not, but I was a boy and a girl." Q. "Why should you want to be a boy?" A. "Not that I wanted to, but I just had the physical change. I can't say I was a boy, but I had a feeling of difference."

She then went on to give some details of her experiences in New York which she had refused to talk about before. She told these in a pleasant and friendly fashion. She stated that she felt all right now and might as well go home. There was no insight into the severity of her condition, but she appeared contented, took her food willingly, talked to the patients and nurses until two hours later when she fell asleep. On the following days she did not return to the behavior she showed before the amytal injection, but seemed absorbed and rather uncommunicative. When she did talk it was in a low tone of voice. These periods of quiescence would alternate with outbursts of excitement and apprehension. During these she sometimes spoke of her body shrinking to the size of a baby and of hearing voices talking about sexual matters. Another administration of sodium amytal resulted in a repetition of the picture described above, only she spoke this time of visual hallucinations.

(2) Sometime later she was given 15 mg. of cocaine hydrochloride at 7.00 a. m. She was quite resistive to the injection. At 7.15 she became restless, jumping up from the bed, lying down again, and pulling on the bed sheet and at her fingers. She had a gross tremor of her hands, a pulse rate of 120 to 140, and a pronounced mydriasis. Her attitude was antagonistic, and she soon began to talk more to herself than to the examiner: "I have the power to call everybody. My mother has the power over me. I told everybody in this hospital doubly twice in both of the rooms not to eat any more, and I meant it." At 7.30 she received 20 mg. more of cocaine hydrochloride. Her expression changed to a more pleasant and dreamy one, she lay quietly for a while, then got up suddenly and went to look out of the window. She did not respond to questions. About 7.45 there was an increased restlessness. She began to walk about and talk. "I think people ought to keep their two voices. Have you heard the birds just talking now? If you are not hungry, you would like to hear the birds speak again." Then she lay down on the bed, covering herself carefully with a pillow and blanket, and seemed absorbed in dreaming. She appeared to be listening to auditory hallucinations. Suddenly she jumped up and asked the examiner: "What do you see outside? I don't believe you. I have tried to call my mother to tell her not to eat any more . . . . . My mother is the 'sunny star.' She is the kindest person all over creation. Her daughter sees this is the 'sunny star' to give my mother the right to keep the 'sunny star.'" She continues in her excitement: "They are the white and the colored. My mother has the power of showing true religion." At 8.10 the patient was extremely impatient, moving around aimlessly. "When I said stop eating I meant it. I told everybody not to eat. I can go out and do what I please." She suddenly approached the examiner as if she was about to hit him. "Are you hungry? Could you eat a beautiful . . . . could you eat human flesh . . . . could you eat? Will

you get my mother?" At 8.30: "This goes right on to the state. Will you please have somebody take my arm? Can't I phone? Call a cab for me right away." She suddenly changes her attitude, relaxes, and states: "All right, I will stay a little while longer. I am planning to help everybody." She continued in the state of excitement and combativeness for another hour. At 11.00 patient became quiet preoccupied and uncommunicative, very much as before the drug was given.

(3) A week later she was given .9 gm. of cannabis indica. No change was noted until after about an hour, when there was a definite dilation of the pupils, a pulse rate up to 120, and flushing of the face. She was uncommunicative, looking at the examiner in a dreamy fashion but not answering any questions. Occasionally she giggled to herself, at times breaking out in loud laughter. Every now and then she would get up and walk in a staggering gait to another chair in the room. As she did that she would look back over her shoulder and make grimaces at the examiner. She ate willingly but was entirely mute until the evening, and then her only response to questioning was: "I want to go home. What is the point of staying around here?"

Two weeks later she was given .2 gm. of mescaline sulphate at 4.00 p. m. and a subsequent injection of .3 gm. at 5.00. Before this she had been answering questions in a fragmentary fashion. Now she became mute and motionless. She was apparently intently absorbed, did not carry out commands, and showed a definite catalepsia. When put on her feet she maintained the position and offered a mild resistance to any effort to move her. Her facial expression was that of complacent serenity. No communication was obtained from her. The next morning the patient reported that she had seen Joseph and the Angels and had heard beautiful music. No other communication was obtained.

CASE IV.—L. A., a 21-year-old single, white, American male, who has shown a decline in interests and ambitions for the last two years. There were instances of psychoses and psychopathies in the family. The mother is of a cyclothymic type; the father, schizoid, with a resulting disharmony and tension in the home. The mother always took the patient's part against the father and complained to the patient when he was still young about the father's brutality. She slept with patient in order to have the father stay away. The father, according to the mother, has never liked the patient, and this hostility between the father and son has grown worse, so that during the last year the patient would go to bed and refuse to join the family as long as the father was in the house. Physically the patient has a congenital hernia and undescended testicle. He has always had marked digestive disturbances and feeding difficulties, apparently on a functional basis. He continued "baby talk" until school. He grew up to be a quiet, shut-in, suspicious adolescent who did not take part in athletics because of his hernia. In March, 1931, the hernia was closed and a small undescended testicle removed. This operation marked the onset of his present illness. He became seclusive, impulsive, and silly in his behavior, began to walk in an affected fashion, revoked many of

his statements when they were just made, and began to be careless about his appearance and reckless in driving the car. He then began to quarrel with the father and threaten him. On admission the patient was found to be in good physical condition. He showed a tendency to grimacing, paced the floor restlessly, appeared apprehensive, at times friendly and at others suspicious. He would suddenly slap physicians, attendants, and patients. He talked in abstract phrases with inadequate affect.

EXPERIMENTS.

(1) The patient was given 6 gr. of sodium amytal intravenously. Almost immediately he showed a marked degree of relaxation. "This is swell. I like that. What kind of stuff are you putting in there? You are a swell guy any way." Patient becomes quite talkative, reporting freely and in detail the difficulties that led to the onset of the illness. He has changed ever since the operation. "Everything looked dark to me. Nobody seemed to like me any more. Before the operation I always thought I could not get along because I had to worry about the rupture. Afterwards there was nothing to do." He states that he has always been self-conscious about the absence of one of his testicles. He felt different from the other boys. He was afraid of other boys, yet he liked to fight them. He remembers one fight when about eleven in which he made it a point to be beaten up by another fellow. He liked to sneak in on sexual play of other boys and would get beaten up by them if discovered. He took special interest in watching dogs at sexual activities. When he was eleven an older boy had sexual relations with him per rectum. He found it disgusting. He thought he couldn't have any friends. Lately he felt waves of rage and madness come over him which he couldn't control. Patient has considerable insight into the nature of his condition under the influence of the drug. He seemed to be emotionally warm and begged the examiner to do everything he could to get him out of this. After an hour he went to sleep and the next morning presented a typical hebephrenic picture again.

(2) Five days later he was given 30 mg. of cocaine. He became restless, hilarious, and made fun of the stenographer because she was without her glasses. Long silence followed during which the patient pulled at his clothes, looked at his hands in different positions, showed a good deal of grimacing, and suddenly began excitedly: "I feel different than when I came here. Just was going to start to sing, 'There's a Rainbow in the Sky.' That medicine didn't even phase me. I'll tell you, I don't think it is going to do me any good. I would like to fly out of the window. I've lost my faith." He continues in this vein, talking to himself and disregarding the examiner. He produces fragments of memories in a loosely connected stream. Patient's excitement subsided gradually. He became less talkative and very soon was as evasive and uncommunicative as before.

(3) Two weeks later at 9.15 a. m. the patient received .5 gm. of mescaline sulphate. Patient was mute for a long time, it being impossible to establish any contact with him. Then he began to whisper to himself, giggle,

wrinkle his forehead, and look around with apprehension. Later he began to open and shut his mouth as if trying to bite somebody, and then blowing out air in big puffs. At times he sighs, whispers indistinguishable words to himself, and at others he laughs. He strokes his hair and sits up in bed in a stiff fashion. Examiner calls his name several times. He answers loudly, "What?". Q. "Is the world changing?" Patient whispers, "I see most of my life." Further questions are only answered with "what," or "I don't know." He keeps on staring into space, quite unable to communicate anything about his experiences. He seems deeply absorbed. There is no catalepsy and no increase in muscle tonus. During the next two days the patient was unusually uncommunicative and unwilling to give any information about experiences with reference to the drug. "Hard to recall those dreams I had."

(4) A few days later the patient was given .9 gr. of cannabis indica. After 50 minutes he showed restlessness, paced the floor, showed increased grimacing, seemed antagonistic, and unwilling to communicate anything about his experiences. He had been observed the preceding day trying to hide knives in his napkin. When asked about it he stated, "It was a funny incident. I suppose they thought I wanted to stab somebody." (He laughs loudly.) Nothing was learned during or after the medication about his real experiences. He seemed to be more suspicious and usually sat in the corner of the room by himself watching everybody, gritting his teeth, and clenching his fist.

CASE V.—W. B., a 40-year-old man. Diagnosis: Psychoneurosis. He was admitted because of depression and marked speech defect in which he produced barking sounds instead of articulated speech. His development was that of a sensitive boy, lacking in self-assurance, and with an inclination to psychoneurotic reactions. He married a woman older than himself who managed things for him and was rather critically disposed. He was unable to work as well or to earn as much as she expected him to. Two years before admission he had had a minor car accident which led to temporary unconsciousness. After the accident he became more sensitive, and at times irritable and easily depressed by his wife's usual critical attitude. He became more and more religious, went to numerous meetings, and six weeks before admission he developed his illness directly after a sermon. He became bewildered and went into a state of panic, had frightening dreams, began to state that the Lord and devil were fighting about him, and began to substitute barking, bellowing sounds for his natural speech. This made it impossible to get any communication from him of his experiences. For several months he was in this hospital, improved slightly, was paroled home, but returned with his old complaints.

EXPERIMENTS.

(1) After several months of attempts at establishing rapport with him he was given 3 gr. of sodium amytal. Under the influence of the drug he lost his tension, began to cry bitterly, and communicate significant facts. His speech difficulty disappeared. "The Devil tempted me. For nothing in the world will I ever let the Devil tempt me again. I always had to keep this

secret, even from my wife, and now I dreamed about it all. After I learned from the Bible what it was, I thought it was terrible. I had a little dog. I never had anything to do with dogs but dreamed about it. I read about it in the Bible and it kills me." (Patient cried bitterly.) "In the old law for laying with an animal you could be killed. Sure it was meant for dogs. I thought it would be best for my children to be killed. It just about breaks my heart." The patient went on with this type of communication. The emotional reaction was still very marked after the drug effect had worn off. Patient then began to be much less tense than before the administration, and it seemed to have had a cathartic effect followed by rapid improvement. He got along well at home until his wife obtained a divorce, when the patient again developed his speech defect. He was readmitted and immediately improved so that no abnormality of behavior or expression could be discovered after a two weeks' stay here.

(2) About six weeks later he was given 30 mg. of cocaine. He began to cry bitterly, talk to himself, complaining about his wife's attitude. "She tried to get rid of me. I suppose I ought to have taken her more placidly than I did. She said we were never properly mated. She tried to bring up the kids right, and I have too. I backed her in everything, but she hasn't done right. When I came back she said she bawled while I was gone. She went out with the beauty operators on Sunday and didn't get back until after midnight. I bawled and she apologized." Patient showed no change outside of his restlessness and talkativeness. In his communications he seemed to be talking to himself rather than addressing a person who was listening to him.

(3) Two weeks later he was given .9 grams of cannabis indica. After an hour he showed dilated pupils and a pulse of 120. He lay down on the couch, cried, and complained of dizziness, exhaustion, and unsteadiness on his feet. He spoke in a weak, tired tone, with difficulty in articulation and occasional recurrence of the old speech defect. He appeared depressed, sad, and complained of pains all over. He "could not think straight, everything seemed dark, but he did not see any pictures. Things looked very natural, just a little small." An hour later, patient's pupils were different in size. His movements and gait were slightly ataxic. He felt "all knocked to pieces," and wanted to go home to his mother.

(4) On the next day he was given .4 gm. of mescaline sulphate at 3.30 and 4.30 in equal doses. He became definitely depressed and cried profusely for twenty minutes. This was followed by preoccupation, after which he was quiet and cried again, "What are you doing to me? It feels like I am going into a trance. I don't know whether I am doped or hypnotized. What's all this? Feels like riding in something." Suddenly he laughed and giggled, and then began to talk rapidly. "People look like dogs. Small statues, midgets. I am half dead. My head has a numb, puzzled feeling. (Patient cried again.) No one can tell how it feels. My reasoning has been taken away." In a few moments he made barking sounds, and ten minutes later said, "I was thinking back home. I just can't control myself." He estimated the time since the injection correctly. "I am going to faint. Give me some smelling salts. I

am about as weak as any man can feel. My brain is in so many different stages. You don't look natural to me. You look tall and thin." Patient knelt down and prayed, crying. He became very excited. "I have been traveling now in space for a year. This is eternity. Won't somebody help me? Can't you help me? Something about personality, personality, personality, personality. You made an impression on my mind. You gave me a vision of something. Something is distinct in your personality. Some people have a personality. Get me out of this space. They put me into space. I am going out of existence. For a number of minutes he was absorbed, then prayed again. "God knows me. He takes care of me. Please don't keep so distant from me. Get me out of this eternity of space, be myself again." Thirty minutes later: "Where am I at?" He jumped up, wanted to get hold of anything around, pulled persons to see if everything was real. "Please help me to get out of here. I want something substantial to hold on to. I am dead to the world. I am gone. I want real life, no imaginary stuff." He continued in a similar fashion for several hours. The next morning he still had a feeling of distance from other people. He was grateful that things seemed real to him. He would not have the same experience for a thousand dollars, but he was willing to give an account of his experiences to psychology students. The point stressed mainly was the feeling of unreality which troubled him.

CASE VI.—V. W., a 28-year-old white American male. Diagnosis: Psychoneurosis. He was admitted in a state of dramatic, theatrical excitement in which he had claimed he made an effort to convert everybody to the true religion. Patient was the sixth of eight children in a farmer's family which was free of mental disease. He was a small, shy child, had violent temper tantrums, but enjoyed being with other children. He was considered as lacking in initiative and remained somewhat dependent upon his own family. Two years ago he married an unattractive, pugnacious woman who tried to manage the home. The patient has a phimosis which has worried him a great deal. He was afraid to see a physician because of fear of an operation, and on several occasions tried to improve the condition by his own manipulations. He continued masturbation after marriage, and the marital relations were unsatisfactory to him. Four weeks before admission here he began to read the Bible and found a passage with reference to circumcision. He claimed that he was justified to perform circumcision on himself, and he proceeded to do so afterward. His wife, who had objected to it, produced proof in a dictionary that it would cause impotence. From then on patient became excited, claimed to be destined to be a religious leader, threw himself on the floor, prayed, sang, cried in a theatrical fashion, and was brought to the hospital in this condition. During the first days he preached and was so noisy he had to be restrained. He appeared apprehensive as soon as anybody approached him and spoke about the unholiness of his surroundings. Within ten days he quieted down. He stated that he had been unable to cure another patient by fasting two days and feared God had withdrawn the mission from him. Since then he became cooperative in examination and showed orderly behavior. He was un-

willing to communicate the true situation, and when approached about his sexual troubles, he had a tendency to slide back into his religious performances.

EXPERIMENTS.

(1) The patient was given 6 gr. of sodium amytal. He became friendly, quite communicative, and began to talk about his experiences during the last year. He began by saying that he was always somewhat embarrassed by his sex organs. The phimosis troubled him before marriage, but he was afraid of the doctors and preferred to do the operation himself. He expected more satisfactory intercourse to follow that. He was afraid of telling his wife beforehand because she might object. He tried to convince himself that the Lord wanted him to do this. He looked through the Bible trying to find a statement supporting him. On admission to the hospital he was afraid mainly because he thought that he might be pronounced insane. "I thought everybody here was awful. The men put me in cold packs." Following the experiment the patient continued to show a friendly attitude, and even joked about the fact that he was so apprehensive during the first part of his stay here.

(2) Sometime before this he was given 30 mg. of cocaine subcutaneously. He became excited, restless, seemed dissatisfied, annoyed, and demanded to be discharged. He began to talk in a stereotyped, sing-song fashion, in the same manner as he had upon admission. The productions were superficial and concerned his religious ideas and plans for world reform. At the end of two hours the effects of the drug had worn off and he seemed quiet and complacent.

(3) Four days after that he was given 9 gm. of cannabis indica before breakfast. He became very antagonistic and began to talk in an excited way, stating that he was moved by the Holy Spirit. He still believed he was right when he came here and was brought here for religious persecution. He would not, however, discuss personal affairs. No information was gained about unusual experiences. The patient remained antagonistic and assured about his religious mission throughout the period of the influence of the drug.

(4) Two weeks later he was given .5 gm. of mescaline sulphate. He became absorbed, quiet, and did not answer questions for more than an hour. He sat on his bed in a stiff position as if trying to fight something off. Suddenly while the examiner sat near him the patient jumped up and exclaimed, "You are not going to get me. This is not getting a hold of me. You are not going to dope me." He sat down again in his stiff posture. As the examiner was leaving the room, the patient began to walk along the crack in the floor. He continued to be tense and uncommunicative, and only at the end of another hour he shouted at examiner: "Things look dark. That's all. You are not getting me. I don't believe this should be so. There is no change in my body. Nothing outside." The only communication was his assurance that everything looked natural. At 11.30 he got up, stood erect before examiner, and said, "My views have been established now. In my own conscience I have made up my mind. My wife is out there. She needs my care. God

has sent me on this mission. I can go now. He has proven it to me. He has performed a miracle. Your dope never bothered me. I never felt better in my life. God Almighty has dealt with me. The Lord be praised. He helped me from the double shot. It didn't affect me. Things look natural. I feel better. There is nothing the matter with me. All the dope didn't bother me. The water doesn't look black. I am going to help people. God has saved me." The patient then became uncommunicative again, and it could not be ascertained whether or not he had any hallucinatory experiences.

Comments.

Before we approach the discussion of these results, we would like to summarize briefly the findings in our subjects. The first four patients were cases of schizophrenia; the last two were psychoneurotics. All of the schizophrenic patients represented fairly uniform material because they had all gone through the acute phase and had settled down to a more or less complacent attitude in which they had made some form of adjustment between reality and their fantasies. Their reaction to the different drugs was as follows:

Case I responded to *sodium amytal* by abandoning her fantasies while the effect lasted and by accepting the examiner as a friend and communicating a coherent story about the development of her fantasy life. In this communication she used the language and logical sequence characteristic for normal social intercourse and only occasionally for very short periods permitted herself to return to her playful fantasy. Under the influence of *cocaine* she became excited, had a marked emotional outburst, with a rapid stream of talk in which she was talking more to herself than any outside person. In this, fragments of reminiscences and hallucinatory references were intimately intermixed. The intensity of her abnormal experiences seemed to be increased. Her utterances gave information about changes in her own body and in the outside world which had not previously been communicated. Under the influence of *cannabis indica* she was quiet, dreamy, and more absorbed in her abnormal experiences than usual. After the administration of *mescaline sulphate* she had a marked increase in her hallucinatory experiences and also a number of new perceptual phenomena which could be recognized as typical of this drug. The experiences were elaborated upon as part of the usual fantasy world, and the examiner was drawn into this world. The changes were woven into her paranoid interpretations.

Case II. This patient was in a stage where he had shifted from a state of intense absorption and intensive hallucinatory experiences into one of emotional shallowness and superciliousness before the experiments were done. None of the drugs had any pronounced effect on this man. Under *sodium amytal* he was a little more communicative and reported more about his previous experiences than at any other time. There was no recurrence of hallucinations, and he placed himself in the world of reality, considering his previous experiences as having been abnormal. He showed no apprehension and accepted the physician as a man who was able to help him. The drug never seemed to allow him to give up his reserve. Under the influence of *cocaine* this man was self-assured and insisted upon the validity of his experiences, criticizing the hospital and demanding to be left alone. He communicated some of his experiences with the air of a person who did not need to fear any objections. The material obtained with the other two drugs was not sufficient on which to base any conclusions.

Case III, who was first examined during the period of transition and later after she had made a hebephrenic settlement, showed the following reactions: *Sodium amytal* at the early experiment produced a state in which the patient talked in a plausible manner, using the ordinary logic and giving up her elaborations in favor of an evaluation in keeping with the standards of reality. She found reasons for her behavior in her own development and accepted the physician and other persons as sources of help. She was, however, unwilling to communicate emotionally relevant material of a deeper level. Her rationalizations were very superficial, though in keeping with normal logic. At the second *sodium amytal* experiment she still used the logical sequences of thought, but her communications were less coherent and less complete. Under the influence of *cocaine* she became aggressive, demanding, self-assured, criticized the outside world for not accepting her proposals, which she now did not recognize as psychotic, and communicated cannibalistic desires as if she had lost the appreciation of their incompatibility with human standards. Under the influence of *hasheesh* she was absorbed, enjoyed giggling, and numerous expressions of delight. Under the influence of *mescaline* she showed a profound regression to complete absorption and catatonic withdrawal.

Case IV. *Sodium amytal* induced this patient to give up his apprehensive, antagonistic attitude which was based upon a masochistic trend. He communicated important facts which have conditioned his attitude. He gained insight into his condition and seemed to make an effort to establish a type of behavior which fitted into the social world. Under the influence of *cocaine* he became excited, restless, considered himself as justified in his abnormal attitude, and demanded recognition and appreciation. This was brought out in a rapid stream of talk, along with a number of fragmentary items which were related to his dreams, and some impressive early experiences which were related to the emotional background for his present reaction. His attitude towards the examiner was distant and critical. Under the influence of *cannabis indica* the patient appeared quiet, absorbed, uncommunicative, and was evasive about his experiences. Under *mescaline* he was less guarded, but his statements referred only to changes in his own body. He showed no interest in the outside world.

Although there were some striking similarities in the reaction of these four patients to these drugs, there were, nevertheless, definite differences apparently related to the patient's personal problems and mode of adjustment. Thus in Case III, who had not before entered the catatonic state, there was a regression to this level under *mescaline*. She also showed a very marked reaction to all the other drugs. Her productions were manifestations of her level of regression and showed very few signs of the typical changes in perception which usually are characteristic of the different drugs. Case I also showed a very marked reaction to all of the drugs, having a reverse of her regression to the logic of normal life under *sodium amytal* and a profound absorption under *mescaline*. Here, however, we could follow the symptoms characteristic for *mescaline* intoxication which were taken into her usual system of pathological experiences, without insight into the true cause for the change. The productions, of course, belonged to the range of the experiences characteristic for her personal psychotic adjustment. Case II showed very little reaction to any of the drugs. He has come through a catatonic state, and his emotional response was very limited. His complacency was interrupted only under *cocaine*, where he demanded his release. With none of the psychotic patients did the drugs produce any states in which something

entirely new without definite interrelation to the pre-existing symptoms was observed. Furthermore, none of the four psychotic patients showed any reluctance in accepting the effects produced by the drugs.

The two psychoneurotic patients differed somewhat in their reactions to the drugs. The effects of *sodium amytal* were the most consistent and also the nearest to those observed in psychotic patients. Under this drug most patients reveal important facts in their life and give up the reserve and shame which has kept them from facing their unpleasant experiences and their difficulties. There was also some similarity in their recations to *cocaine*. The patients showed a mild degree of excitement, but there seemed to be a definite reluctance to accepting the change. Both patients felt unpleasant, "doped," interfered with in the usual control of their mental functions. They both, however, became more demanding, aggressive, and critical, just as the psychotic patients. The reaction to *cannabis indica* showed to a more marked degree the reluctance to the acceptance of the change. The complaints in both patients were of a psychoneurotic nature: complaints about the state of their body, fatigue, dizziness, vague pains, and unwillingness to indulge in elaborations on the changes in perception which would be made possible by the drug. Under the influence of *mescaline* both patients showed a marked reaction. One of them tried to suppress all evidence of changes in reality and prayed to the Lord for help to ward off the effect of the "dope." The other patient was drawn into the change of reality but with a definite expression of horror and bewilderment and was continually reaching out for deliverance from this state through the examiner. It must be stressed here that under the effects of this drug there was a reappearance of those symptoms from which the patients had been freed by the treatment: in the first case the speech defect and depression, in the second the religious conversion.

It would seem then that under the influence of *sodium amytal* the patient shows a decrease in his critical judgment with reference to the condition of the world of reality. Social standards and difficulties seem to be less oppressive. He feels emotionally nearer to the representatives of the outside world, is able to identify himself with other people, and communicates freely because he does not fear any criticism from them. This condition is not unlike

that in the state of hypnosis, where the critical judgment about the state of affairs in the world of reality is left to the hypnotizer whom the subject endows with his ideas.

Cocaine which superficially also leads to an increase in the patient's readiness to communicate seems to do so on a different basis. Here the subject, who previously felt more or less uneasy about his own abnormal experiences on the basis of the fragments of critique which were still left over, will now stand up for his own level of regression and communicate with arrogance and aggressiveness his experiences. He seems to identify himself with his level of regression.

Under the influence of *hasheesh* new experiences are created which allow new presentations or new fantasies and an increasing neglect of the outside world in favor of experiences which are in keeping with the person's desires. The patient is absorbed and uncommunicative. He is apprehensive and afraid of being ridiculous.

Finally under the influence of *mescaline* the level of regression is still lower. The new experiences are utilized for more primitive reactions. The physician as well as the representatives of the environment are drawn into the world of fantasies, and the rationalizations are in the system of the logic characteristic for this level of regression.

In order to bring out more emphatically the changes characteristic to the different drugs we have tabulated them in the following chart: (See Chart 1.)

In contradistinction to the above considerations and as a supplement to them, let us turn to the difference in the effects produced by these drugs in different conditions and individuals. For this purpose we will have to consider the following points:

(1) How do our findings compare with the reactions observed in normal persons? A number of reports are available in this field. The effects of *sodium amytal* on normal persons were studied by one [11, 12] of us. They were shown to be essentially the same as we observed in our clinical material, with the only difference that in schizophrenics the emotional response is, naturally, not quite as pronounced as in normals or psychoneurotics. The effects of *cocaine* on normal persons were studied by Mayer-Gross,[14] Frankel and Joel,[5] and Jacobi.[6] These consisted in impulsive outbursts,

	Reactions.	Sod. Amytal.	Cocaine.	Hasheesh.	Mescal.
1	Changes in PERCEPTION.	No change.	No change. In Schizophrenia increased vividness of falcifications.	Distortions in space and time.	Hallucinations.
2	Direction of AFFECT.	Outward.	Indifferent with self assertiveness.	Inward (Narcissistic).	Inward (Narcissistic).
3	CONTACT.	Good.	Unchanged.	Poor.	Normal—varies. Psychoneurotic: Search for help. Schizophrenic: Lost.
4	COMMUNICATION.	Increased for all contents.	Increased for psychotic manifestations. Decreased for underlying events.	Decreased for all contents.	Decreased or colored by elaborations.
5	ANXIETY.	Absent.	Normal—present. Psychoneurotic: present. Schizo.—compensation.	Present.	Normal—varies. Psychoneurotic: present. Schizo.—absent.

CHART 1.—Reactions Characteristic to the Different Drugs.

aggressiveness, and very rarely hallucinatory experiences. (We must remember, of course, that in both of the above drugs, as in a good many others, the chronic addiction brings in a number of other possibilities.) The effects of *hasheesh* in normal persons were studied by Frankel and Joel, Kant, and one of us. The outstanding features were the space and time disturbances, but with that there were also tendencies to paranoid interpretations, self-absorption, and, occasionally, impulsiveness. Finally, the effects of *mescaline* on normal persons were reported by Beringer and a number of other authors. Here profound changes were obtained, such as sense deception, emotional distance, and self-absorption.

(2) How do our findings compare with the observations made by other authors of the effects of these drugs on mentally diseased persons? Here, too, the observations made in the case of *sodium amytal* were similar to some of our findings. *Cocaine* was used by Berger,[2] Fleck,[4] Jacobi,[6] and others. They reported that catatonic patients and cases of milder stupors became excited and began to talk under the influence of the drugs. Furthermore, we find the same aggressiveness and impulsiveness. In the case of *hasheesh,* Kant [9] observed in schizophrenics an increase of the hallucinatory tendencies and, in one case, a recurrence of a catatonic stupor. In depressions during convalescence there was a tendency towards the recurrence of the psychosis. In *mescaline,* Zucker [17] noticed the same increase of the symptoms of the pre-existing psychosis and a tendency towards weaving the abnormal changes produced by the drug into the structure of the psychosis.

In order to bring out more clearly the differences that are introduced into these effects by the conditions present, we have tabulated the most striking features in these changes in normals, psychoneurotics, and schizophrenics in Chart 2.

If we now combine the results shown in the above chart with those tabulated in Chart 1, we come to see the importance of this method of approach to our study. Each drug undoubtedly has certain specific characteristics, but these are quite closely related to the conditions which are present at the time when these specific effects are produced. The changes produced by a given drug will not only be elaborated on in the light of the pre-existing psychic state, but totally new types of reactions may result from such an interrelationship.

Another equally important factor in the molding of the effects produced is furnished by the individual characteristics and background of the person himself. Different individuals, even with the same mental condition, may react differently to any one of the

	Normal.	Psychoneuroses.	Schizophrenia.
SODIUM AMYTAL.	Friendly, serene, emotionally receptive. Willingness to communicate emotionally tinged contents.	As in normals.	As in normals but less communicative and emotionally colder.
COCAINE.	Aggressive, excited. Impulsive outbursts.	As in normals.	The reaction as in normals but colored by psychotic material.
HASHEESH.	Talkative or self absorbed. Tendency to paranoid formations. At times impulsive. Space and time disturbances.	Apprehensive. Decreased communication. Time and space disturbances.	Silent, self absorbed apprehensive attitude. Much less change in space and time perception.
MESCALINE.	Changes in perception with sense deceptions. Emotionally distant. Self absorbed.	Pronounced fear of, and resistance against changes in reality.	Tendency towards catatonia. Increases in hallucinatory experiences. Elaboration of these in relation to psychosis.

CHART 2.—Effects of Drugs in Different Conditions.

drugs. This was seen to be the case in all of our patients. These differences do not only show themselves in the superficial structure of the change produced but reach down deeper into the personality and determine the levels which these effects may reach. A particularly interesting illustration of this factor was seen in a group of

cases in which amnesias of different origins (such as post-hypnotic, post-suicidal, and psychoneurotic) were cleared up under the influence of sodium amytal. With the lifting of the amnesia there also came to the surface a number of facts in the history of the patient that were not obtained previously. The amount, emotional quality, and depth of these facts, however, were different in the different patients, and were closely related to the conditions that in each particular case led to the development of the difficulties.

In addition to the psychopathological effects of these drugs, we were able to establish the occurrence of physiological changes in our subjects. The analysis and evaluation of these are outside of the scope of this contribution, but we cannot forego a brief reference to some of them. One of the most interesting of these was the occurrence of fluctuations in the chronaxie of the muscles. Thus, mescaline produced a marked change in the chronaxie of a patient in whom the drug induced a catatonic state. In contradiction to this, sodium amytal, given to catatonic patients in whom there were definite chronaxie abnormalities, caused a return to normal chronaxie values at the same time as it produced the psychological effects. Looked at in the light of the physiological changes reported by other observers (DeJong's [20] production of catatonic states by the use of mescaline, etc.), these findings open up new avenues of approach along the lines of experimental psychopathology.

Without going any further into the evaluation of the rich variety of facts that unfolds itself in this field of research, we wish to emphasize particularly these two aspects of it. (1) The fact that the psychopathological changes induced by the drugs are definitely related to the whole personality and the situation within which it functions, points to similar considerations in the study of psychiatric symptomatology in general (a point which has been particularly stressed by Schilder [18, 19]). In the investigation of the effects of drugs we will, therefore, tend away from a static description of phenomenological details but towards a dynamic appreciation. The symptoms produced will have to be evaluated, not as isolated primary occurrences, but as resultants of a change in the attitude of the person to reality, as it is changed by the effects of the drugs. (2) The physiological changes that are found along with those of a psychological nature indicate once more the intimate interrelationship of these two components of the individual.

Further work will have to be done before we can come to further insight in this field, but our results indicate quite definitely the value of investigations of this type as well as the lines to be followed.

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DISCUSSION.

DR. HARRY STACK SULLIVAN (New York City).—I would like to take a moment to compliment this fine piece of pioneering in psychobiological pharmacodynamics, and thereafter talk on the general topic of pharmacodynamic research in our field.

From the conception of the person as a psychobiological unit, or abstraction, which is manifested chiefly in interpersonal relations, integrations with others, we can deduce good justification for the clinical, psychiatric application of potent drugs that affect the function of the integrating apparatus. In talking to you here I am more or less integrated with a portion of you in a total situation. If I could give the rest of you some potent drug which would greatly heighten your tendency to be entangled in any stray personal stimuli flowing around you, obviously I would become integrated with more of you. In other words, more of you would hear me and follow me. On the other hand, if I were having a bad time talking to you because I am too closely integrated with negative affects you have toward me, and I should take a drug which would diminish the efficiency of my integrating apparatus so far as stage fright, or anything like that, is concerned I would be, obviously, at an advantage. The psychiatrist is called upon to do something for actively psychotic people. These people are integrated with other people in an extraordinarily unsatisfactory fashion. That is the simplest, soundest description of a psychosis that I know of.

Dr. Malamud, and others, have noticed that certain drugs have a marked effect on what goes on between two people, namely, the patient and the investigator. He has, to his great credit—he and his coworker—attempted to bring some systematic observation into this field. You have heard his results which must impress you as very stimulating. I have something to say as a result of a rather parallel investigation in which I have had a hand chiefly for my personal information.

The clinical psychiatric problem may be stated thus: if a schizophrenic is blocked because he has conflicting motives in dealing with people, and particularly with the psychiatrist who wishes to be of some assistance to him, is it possible, by the use of a pharmacodynamic agent so to disturb the integration that one part of it will continue to function, in other words, one of the motives will continue but the other conflicting ones will be so enfeebled that conflict phenomena and blocking disappear, leaving instead the manifestation of a more or less commonplace intercommunicative set. This can, unquestionably, be done with some people, consistently. In other words, it is possible to pick out a certain type of psychotic schizophrenic to whom certain pharmacodynamic agents can be administered with uniform predictable improvement of contact. Therefore, among other things the notion of usefully disturbing the

activity of the integrating apparatus by the utilization of a pharmacodynamic agent can be demonstrated.

Ethyl alcohol has shown a more uniform and effective therapeutic effect than has sodium amytal, in my hands. Its effect is quite closely related, can be greatly prolonged without material danger to the physiology, and its therapeutic utilization arises from and rests on a vast body of general human experience reaching back into the shadows of prehistory. Ethyl alcohol is the type drug in the psychobiological pharmacodynamics by which to accomplish a blunting of unpleasant aspects of a given interpersonal integrations, with the release from conflict and/or from inhibition of less differentiated tendencies of the personality. The more recent elaborations of the critical self are the most enfeebled in ethanol intoxication.

However, there is another development in this same field. One can now carry the attack on the self-consciousness to the point of complete suspension of relevance of "external" reflections to the self. By the utilization of *tribromethanol,* a perhaps dangerous drug, one can abolish *in toto* all receptivity to externally conditioned criticism, and approximate the somnambulistic state, with its ability to carry out highly integrated behavior—especially speech—without actual discriminative awareness of the other person in the integration. The results that are thus obtainable are sometimes astounding.

Besides this selective disordering of the personality, we can abolish all external reference, as in deep sleep and narcosis. This effect is typified by chloral, chloroform, and the pheno-barbital compounds. Their psychiatric utility is probably dubious excepting in overcoming the evil effects of fatigue, which I have discussed elsewhere.

Lastly, on the reductive side, we can effect deep disturbances of the intrapsychic balance, of none too clearly understood character, as by utilization of the atropine group. There is a good field for pharmacodynamic research here, and we may finally have some psychiatrically useful delirifacients that will facilitate the analysis and reintegration of personality to an almost unimaginable extent. This urgently desirable end, however, must wait on the adoption of a sound theory of personality, as well as on the growth of interest in the psychobiological effects of chemical substances introduced into the body.

Finally, we have some drugs that are more or less uniformly incremential to the integrative systems. The caffein group is an excellent example in relation to the neoencephalic integrator.

These remarks are intended to supplement this excellent paper, particularly with reference to the use of drugs as preliminaries and as adjuvants to psychotherapeutic effort. I have no fond hopes of finding drugs specifically effective in removing defects of personality development. There should be extensive and intensive investigations of potent drugs as to their actual effects on interpersonal relations, as a parallel and mutually effective means for increasing our knowledge of personality and its inadequate and disordered functional activity. We know already that ethyl alcohol and amytal are effective in changing some interpersonal situations from discouraging arrest

to active cooperation. So far, however, as practical clinical psychiatry is concerned, the utility of these drugs still waits on our having something really useful for the patient to collaborate in, once he is thus made ready to begin work.

DR. A. A. BRILL (New York City).—I wish to ask Dr. Malamud why he did not give his patients alcohol? I understand that in this noble experimental age we have to be a little cautious in the use of alcohol in institutions, but I wonder how the patients would have reacted to alcohol. I have done a similar experiment with Jung in 1908, by using the galvanometer on test persons whom we at first gave non-alcoholic wine, and then added some alcohol without the test persons' knowledge. The results were very interesting.

Another question: Could not the same results be obtained by simply talking to the patients, rather by suggestion. I have in mind schizophrenics of the catatonic type, who have been mute—some of them for years—whose attitude and manner changed completely after I took the time to talk to them and urged them to do things.

Bleuler reports similar results by suggestion. Depending on the personality of the patient, would not alcohol and talking give the same reactions as mescaline and hasheesh? For many years I have used very few drugs, and consequently I do not know the effects of these drugs, but I am convinced that ordinary suggestion could probably produce the same results and the same reactions as those obtained in Dr. Malamud's interesting experiments.

DR. WILLIAM MALAMUD (Iowa City).—I am obliged to Dr. Sullivan for his kind words. To Dr. Brill I want to say that we, too, have had experience with alcohol, but thought that the inter-personal relationships produced by alcohol are so well known that they do not deserve to be dignified by a paper in the Psychiatric Association. In response to Dr. Brill's question concerning rapport obtained by talking to the patient in preference to using sodium amytal, I am quite willing to entertain the idea that with some psychiatrists of a particularly appealing personality that may be possible. Personally we have had very little success in some cases as, for instance, catatonic schizophrenics. I dare say that a good many psychiatrists will admit their failure to get such patients to respond simple by talking to them. With sodium amytal, however, we have been able to overcome the handicap of the lack in our personal appeal.

However, I want to emphasize again that I did not report the effects of these drugs here from the point of view of treatment alone, but from the point of view of a description of what happens when the patients are subjected to certain situations, and what relationship these things bear to factors that we know in the personality and the background.

HISTOPATHOLOGICAL FINDINGS IN TWO CASES CLINICALLY DIAGNOSED DEMENTIA PRÆCOX.*

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The question of histopathological findings in dementia præcox has been of considerable interest to psychiatrists because of the dual conception that still dominates the field of the so-called functional psychoses. On the one hand, the functionalists try to explain all the mental symptoms in schizophrenia on the basis of abnormal psychological mechanisms independent of tangible organic changes; and on the other hand, the so-called organicists feel that the mental symptoms might be explained on the basis of organic changes as documented by numerous findings reported.

It is not the place here to review the literature from the standpoint of the histopathological findings in dementia præcox. Since Cheney's critical review of the question in 1918, considerable material has been accumulated and numerous cases have been published in which not only the organic changes of the central nervous system have been described, but the pathology of various other organs as well. The large amount of published material pointing to the existence of organic changes in dementia præcox has been summarized in the three papers of Buscaino. With the desire of bringing forward new facts, the interpretation of which I wish to leave open for discussion, I shall limit this report to two cases which during life have been diagnosed dementia præcox, the histopathological study of which has revealed in both instances definite organic changes of the central nervous system.

* For the clinical history of Case No. 1, I am indebted to the Manhattan State Hospital. For the clinical history of Case No. 2, I am indebted to the Buffalo State Hospital. To all concerned in the clinical study of the cases I wish to express my thanks and appreciation for their cooperation.

Read at the eighty-ninth annual meeting of The American Psychiatric Association, Boston, Mass., May 29–June 2, 1933.

CASE 1.—M. K., admitted to Manhattan State Hospital, December 9, 1931; colored female; aged 18 years; born in Brooklyn; one year of high school; single; Baptist; moderate in alcohol; student.

Family History: First cousin developed a psychosis two weeks after child-birth from which she died in five days. The mother of this cousin (maternal aunt) developed a psychosis, following the death of her husband, which also resulted in her death.

Personal History: She was born 18 years ago in Brooklyn and has always lived at home. Father died when she was three and one-half years old and her mother re-married two years later. The step-father deserted the family when the patient was 11. She was happy as a child and fond of her school, though she had some difficulty with her studies. She had numerous friends among girls but the father of her child was her first boy-friend. Her menses began at 14 and were always regular. When her boy-friend first began paying her attention the mother invited him to call, and left them alone together. As soon as the boy learned she was pregnant he disappeared. She was depressed all through her pregnancy and talked of her boy-friend in her sleep. She was kept at home. Her grandmother advised her to have the baby adopted and she was very much depressed at the prospect and late in her pregnancy decided she would keep the child. She spoke several times of wanting to die. She suffered from severe backache and frequent headache. Throughout her pregnancy she had a habit of spitting and in the last few months she complained of hunger.

Personality: She was always cheerful, friendly, and conscientious. She was not sensitive or quick-tempered but rather easily offended. She took severe likes and dislikes and retained them. She was clean, over-orderly and stingy, but not selfish. She was frank in expressing disapproval. She was an excellent singer and dancer, but bashful in company. She thought very well of herself. She was extremely fond of children and would spend hours minding the babies of her neighbors.

Psychosis: A daughter was born in Harlem Hospital on November 20, 1931. Patient seemed perfectly well. She was contented, but rather anxious lest her brothers and sisters disapprove of her. After 12 days she was returned to the Kate Ferguson Home where she had spent the last few months. A day or so later she became quite excited. She wrote her family a letter in which she said she was a spiritualist and that she was going to find her boy-friend and marry him. The records of the Home state that she heard voices and saw strange things. She was transferred to Bellevue and when her mother visited her there, she appeared terribly frightened and then denied knowing her.

At Bellevue: Admitted December 3, 1931. Her pupils were said to be unequal and somewhat irregular, though they responded promptly. She was dull, listless, bewildered and indifferent, talking in a monotonous, colorless voice. She revealed many auditory hallucinations of a religious type and ideas that she had the power to heal. She said the Lord told her to sing psalms, spirits told her that everybody would be cured and would stay well

for the rest of their lives. She said that her baby told her to make faces. She listened intently sometimes and said that she was waiting for the spirits to communicate with her. She walked about laying her hands on patients and claimed that she could cure them. At times was noisy, disturbed and overactive. She said: "My husband is over there on the couch. I hear spirits. The baby told me to make funny faces at its father." She said the Lord repeated the first psalm to her. She said it was the Kate Ferguson Home. Other than this no data are given regarding her orientation.

At Manhattan State Hospital: Admitted December 9, 1931, with a temperature of 101, a pulse of 140 and respirations 22. There were no other abnormal physical findings. She was very excited, profane and obscene. She spat continuously, rolled her eyes and stuck out her tongue. She paid no attention to questions. She spoke of seeing a dog.

A physical examination done on the following day showed a temperature of 100, pulse rate of 130 and a blood pressure of 108/82. Her pupils were somewhat sluggish. She was incontinent. Other than excitement no cause for the fever was discovered. Her urine contained a trace of sugar, though a specimen taken five days later was negative. Blood sugar 105 mg. Blood urea 45 mg. per 100 c.c. Blood taken on December 15, showed a hemoglobin of 60 per cent. Red cells 4,130,000; white cells 13,400; polynuclears 83 per cent; lymphocytes 11 per cent; eosinophiles 5 per cent; basophiles 0.9 per cent. Blood Wassermann negative.

A mental status was done on December 10. She was much emaciated and extremely restless. She frequently got out of bed and went to the window. She scratched and bit the examiner to the best of her ability. She spat in all directions. At times she was quiet for short periods. Often she rubbed her face over the pillow, pursed her lips, and made sucking motions with her tongue. This was followed by repeated snapping of the jaws. She was incontinent. At times she masturbated in the presence of others. She took fluids voraciously. At times she was mute and at other times totally incoherent. She was exceedingly fond of obscene expressions and frequently used stereotyped phrases over and over. Her answers were usually irrelevant. Though her behavior at times was strongly aggressive, her aggression would stop the next minute for no apparent reason. She expressed delusions of a varying character and auditory hallucinations, though her incoherence made it impossible to obtain a clear idea of them. She said the Lord had talked to her but she would not say what he said. She nodded when asked if he had done miracles and then exclaimed, "He shot me in the eye." She frequently asked for ice-cream and said that she had healed her brother-in-law of a mole. She said that she saw spirits. She said that her child was born in Brooklyn Hospital, whereas it was born in Harlem Hospital (she herself was born in Brooklyn Hospital). All questions regarding sensorium were ignored or answered irrelevantly.

Subsequent Course: She became gradually weaker. She continued to vary between moods of violent excitement and relatively quiet states. She was usually incoherent and incontinent. On December 13, she recognized her mother and her cousin but abused them obscenely. She continued to take

fluids greedily. On December 15, she became mute, occasionally moving her arms around her head, rolling her eyes and smiling. She remained mute the next day, but when left alone removed all her clothes and sat on the bed making grimances. She continued to spit in all directions. On December 17, was far less restless and much weaker. Her pulse was almost imperceptible though her heart sounds were of fair quality. Her hands became cold. She repeated several times, "My poor mother," and said she felt very sick. When her cousin visited her, she spoke with great difficulty and somewhat thickly. She asked for ice-cream. For the first time there was ocular incoordination. The right eye tended to turn outward, but came back into the regular position when she looked at things. For several hours before her death she did not speak but was able to drink water shortly before her death. She did not enter into coma but quietly stopped breathing on December 17, at 6.05 p.m. Cause of death: Catatonic excitement; exhaustion; congestion of the brain.

*Differential Diagnosis.**—We have a psychosis of sudden onset two weeks after childbirth. There is no definite information concerning her sensorium in the early part of the psychosis, though it seemed definitely impaired at this hospital. The early part of the psychosis was characterized by auditory hallucinations and delusions concerning the ability of performing miracles. She is described in Bellevue as dull, listless, bewildered, and indifferent. In this hospital her state varied between extreme excitement with a definite tendency to stereotypy and relatively quiet states in which she was often mute. If the psychosis is to be considered psychogenic the diagnosis of catatonia seems indicated in spite of a rather favorable personality and the fact that she was definitely depressed during her pregnancy. There were several organic factors. She did have a somewhat elevated blood urea and the autopsy revealed a definitely edematous and congested brain. The fact that the psychosis began suddenly two weeks after childbirth tends to indicate that toxic factors related to the childbirth are not primary, though it is by no means conclusive. The cystitis found at autopsy is not adequate to account for her death. The present examiner prefers diagnosis of dementia præcox, catatonic type.

Diagnosis: Dementia præcox, catatonic type.

Heredity: Cousin died in post-partum psychosis. Aunt died in psychosis following death of husband.

Etiology: Birth of illegitimate child.

* The differential diagnosis is part of the clinical history as offered by Manhattan State Hospital.

Personality: Sensitive, friendly, active.

Duration: Seven days.

Condition: Patient died December 17, 1931, at 6.05 p. m. Cause of death: Catatonic excitement; exhaustion; congestion of the brain.

Autopsy: Heart was slightly dilated, but otherwise not grossly abnormal. Lungs were somewhat congested but there was no pneumonia. Kidneys were grossly normal. Bladder was very much contracted with a thickened wall and contained pus. The uterus showed no evidence of infection. The liver and the adrenals were grossly normal. Stomach was somewhat dilated. The aorta was very small. Thymus was absent. There was no glandular enlargement. The brain showed definite congestion of the superficial vessels with moderate edema of the cortex.

Diagnosis: Dementia præcox, catatonic type.

The histopathological study of the case revealed the presence of a diffuse encephalopathy that was more pronounced in the pre-central, frontal, and temporal convolutions.

The encephalopathy was characterized by the following findings:

Myelin Sheaths: All over the white substance, but particularly in the frontal, pre-central, and temporal lobes, there are numerous patches of demyelination which occupy the white matter as well as the boundaries between gray and white matter. The size of the patches of demyelination vary (Figs. 1 and 2). Some patches are small, others have a tendency to coalesce, and others of much larger size occupy most of the subcortical white substance. The patches of demyelination are at times perivascular, but at others seem quite independent of the blood vessels. The origin of the large patches of demyelination is difficult to trace, though some of them seem to be derived from the fusion of minor ones, perivascular in origin.

In the most severely affected areas the myelin sheaths are completely destroyed. In others only a rarefaction of the myelin occurs, whereas in the intermediary stages the patches are filled with fragments of myelin or products of disintegration up to a fine granular substance. Quite often in some of the involved areas swollen myelin sheaths are found disclosing a rosary-bead appearance or undergoing various stages of fragmentation and disintegration (Fig. 3).

Most of the study of the myelin covering has been made with the Spielmeyer method for myelin sheaths. This has been checked, however, by other procedures, such as the Loyez method for the same structure.

Very close to the areas where patches of demyelination are found with the Spielmeyer method, the Loyez method discloses the same degenerative changes of the myelin covering as represented by swelling, fragmentation, and disintegration. It can be noticed that the destruction of myelin sheaths is quite considerable and that the degenerative area is occupied by material which assumes here and there a grape-like aspect. Fig. 4 illustrates the formation of grape-like areas of disintegration coalescing together.

Neuroglia: In correspondence to some areas of demyelination, particularly in the frontal and temporal lobes, there is an increase in the glia fibers as detected by the Holzer method for glia fibrils. Fig. 5 illustrates the increase of glia fibrils occupying an area of demyelination. The glia fibrils are in some areas quite numerous and are also distributed in a patchy manner corresponding to the patchy distribution of the areas of demyelination. The glia reaction is particularly pronounced over the precentral and frontal convolutions where a considerable marginal gliosis may also be observed. Fig. 6 illustrates the occurrence of such marginal gliosis in the precentral convolution. It can be seen that not only the marginal layer of glia is considerably increased, but that there is a slight spreading of the glia proliferation into the second layer of the cortex. Fig. 7 illustrates such an invasion of the proliferated glia fibers over the second and third cortical layers.

Nerve Fibers: With the Bielschowsky method for neurofibrils it is seen that the axis cylinders have undergone acute degenerative changes consisting mostly in swelling, occasional rosary bead appearance, and terminal fragmentation. Altogether, however, the involvement of the axis cylinders is not very pronounced and undoubtedly less pronounced than the involvement of the myelin sheaths. In the most severe area of demyelination, however, a definite reduction in number of the axis cylinders occurs.

Microglia and Oligodendroglia: The microglia elements do not show severe involvement in the gray matter. A tendency of the elements to hypertrophic changes with thickening and hypertrophy of the processes but with no definite transformation into com-

pound granular corpuscles is generally all that is noticed. In the white matter the changes are more acute. Some of the elements seem to have lost part of their processes and have a more roundish appearance. Here also there does not seem to be definite transformation of elements into compound granular corpuscles.

The oligodendroglia elements both in the cortex and in the white substance show definite acute swelling as illustrated by Fig. 8. Swelling of such elements is not uniform all over the brain, but is particularly limited to the frontal and temporal convolutions. There is definite increase of oligodendroglia elements in the white substance and numerous oligodendroglia cells can be seen collected along the walls of blood vessels (Fig. 9). In some areas this accumulation is quite considerable and the expression of a definite pathological condition.

Amyloid Bodies: Amyloid bodies are quite numerous, particularly in the temporal convolutions and more so in Ammons horn (Fig. 10), where with appropriate stain their origin from degenerated oligodendroglia and microglia elements can occasionally be detected.

Nerve Cells: (a) *Disturbed Lamination:* There is a definite decrease in the number of cells which involves particularly the frontal, precentral, postcentral and temporal cortices. The reduction in the number of nerve cells involves particularly the second and third layers. Here and there appear definite interruptions in the continuity of the layer, the break being represented by a large patch in which the nerve cells have almost completely disappeared (Fig. 11). In other instances there is only a considerable diminution of the cells resulting in a more or less conspicuous acellular area.

In the frontal convolutions the loss of cellular elements is particularly noticeable and invades the third layer. A comparison between the involved area and the normal control of the same region brings out more clearly the considerable involvement of the nerve cells (Figs. 12 and 13).

In the temporal lobes there is also great poverty of cells, particularly in the second and third layers. (Fig. 14.)

(b) *Acute Degenerative Changes:* The disappearance of the nerve cells seems at times related to vascular involvement; at others, it takes place through a gradual process of disintegration (Fig. 15). These acute changes are particularly pronounced in

the temporal and frontal cortices. In the temporal cortex they are very diffuse but occupy principally the second and third layers. The lesion is represented by both a pronounced swelling of the nerve cells and by the so-called acute severe change of Nissl, leading in both instances to a gradual disintegration of the cellular elements. All phases of the degenerative process can be followed under the microscope and, here and there, shadows of cells are still found particularly in the acellular areas.

(c) *Matachromatic Substance:* At the boundary between gray and white matter, invading at times the inner layer of the cortex in the frontal, precentral and temporal cortices, numerous metachromatic bodies are found. These bodies have a more or less roundish appearance and stain in a reddish-blue color with thionin. They are found generally free between the cells (Fig. 16). A careful study reveals, however, that some of the metachromatic bodies may originate from a degenerative process of the nerve cells. I am not ready now to go into the details of this process which might form the object of a special investigation as to the type of elements which participate in the formation of the metachromatic substance, but I am ready to state that some of the above-mentioned bodies seem to be derived from degenerated nerve cells.

Blood Vessels: The large blood vessels appear to be free from degenerative changes, whereas the small cortical arteries show here and there a process of thickening of their walls through a multiplication of the endothelial elements.

Fat Products of Degeneration: Very little fat accumulation is found surrounding the blood vessels particularly in the demyelinated areas.

In summarizing this whole case, I may say that it has all the ear marks of a diffuse degenerative process which might be labeled as diffuse encephalopathy. The process is undoubtedly a degenerative one as no trace of inflammatory reaction has been ever found either in the meninges or in the brain tissue itself. As to the nature of this encephalopathy, it is a difficult question to answer. I am inclined to consider the process a toxic one comparable to some of the conditions that we can reproduce experimentally through the use of exogenous toxic substances.

FIG. 1.—Patchy areas of demyelination. Spielmeyer method for myelin sheaths—precentral area.

FIG. 2.—Large area of demyelination. Spielmeyer method for myelin sheaths—second frontal convolution.

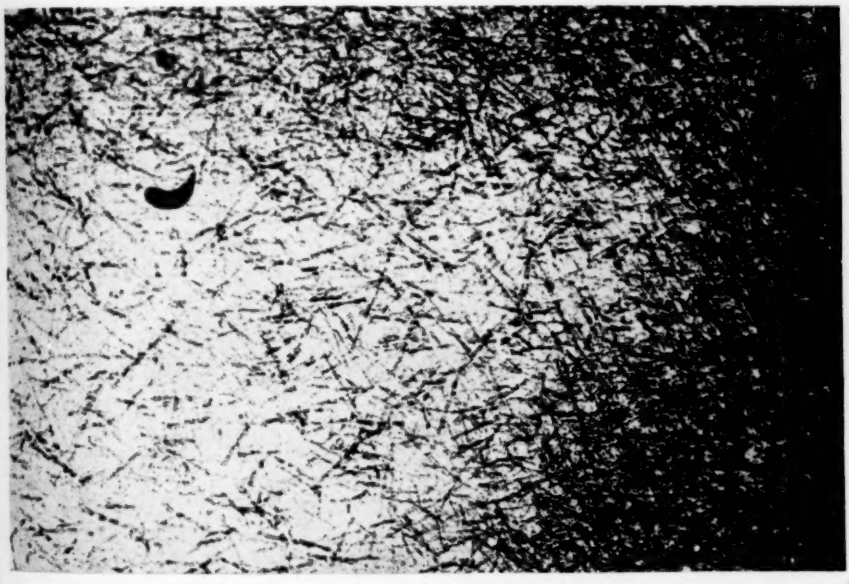

FIG. 3.—Details of an area of demyelination where a few swollen myelin sheaths are still seen crossing the section. Spielmeyer method for myelin sheaths.

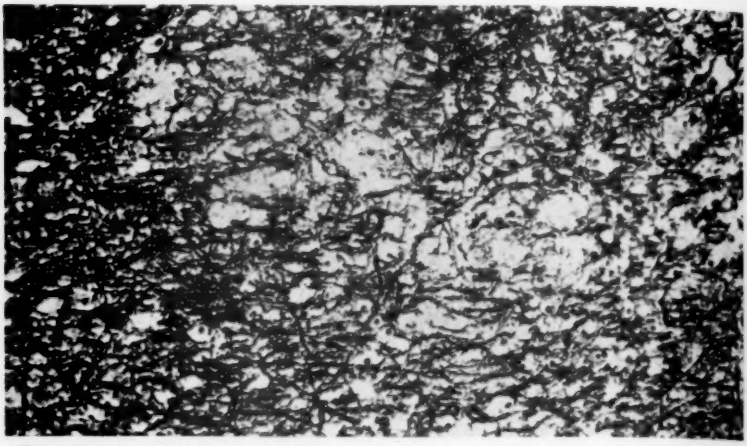

FIG. 4.—Grape-like areas of disintegration of the white substance. H & E stain.

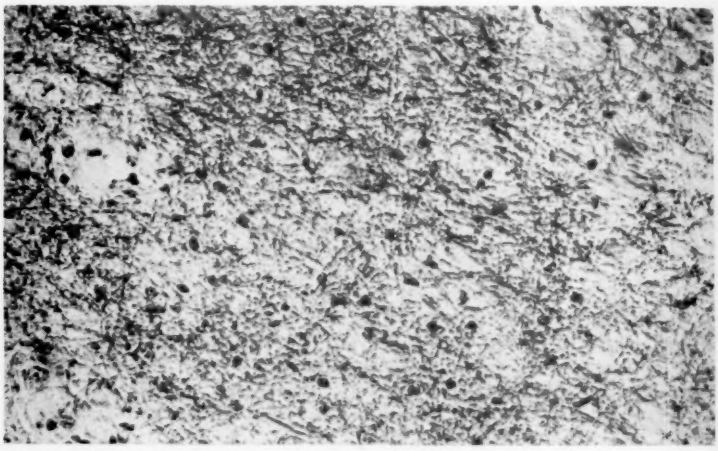

FIG. 5.—Moderate amount of gliosis of the white substance. Second frontal convolution. Holzer method for the glia fibrils.

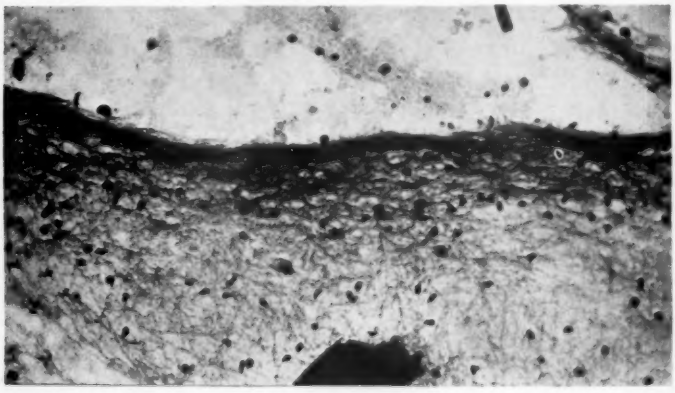

FIG. 6.—Definite marginal gliosis in the precentral convolution. Holzer method for glia fibrils.

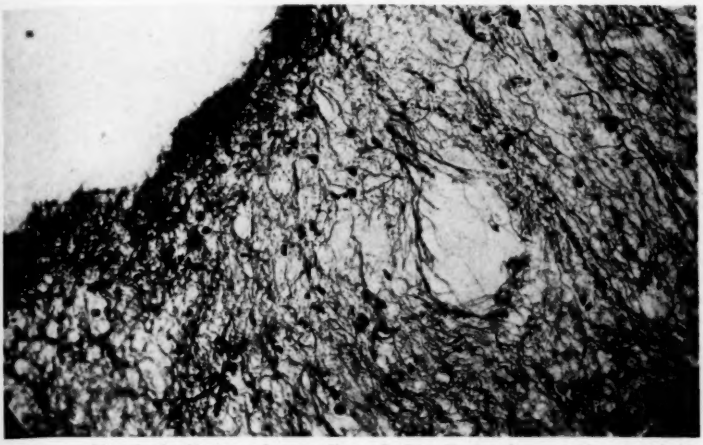

FIG. 7.—Marginal gliosis and spreading of the glia in the second and third cortical layers. Holzer method for glia fibrils.

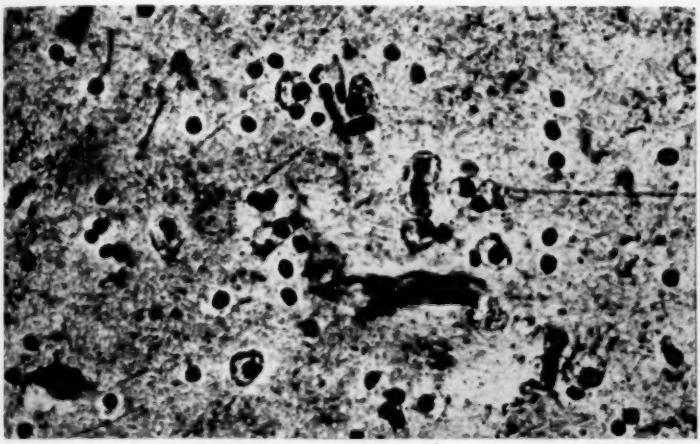

FIG. 8.—Acute swelling of oligodendroglia cells. Globus-Penfield modification of Hortega method.

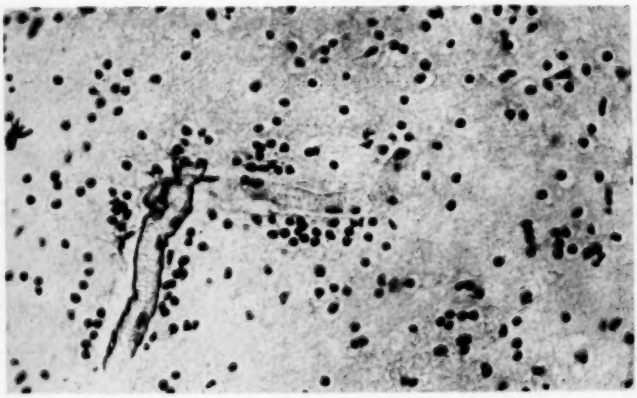

FIG. 9.—Accumulation of oligodendroglia cells around the blood vessels. Nissl stain.

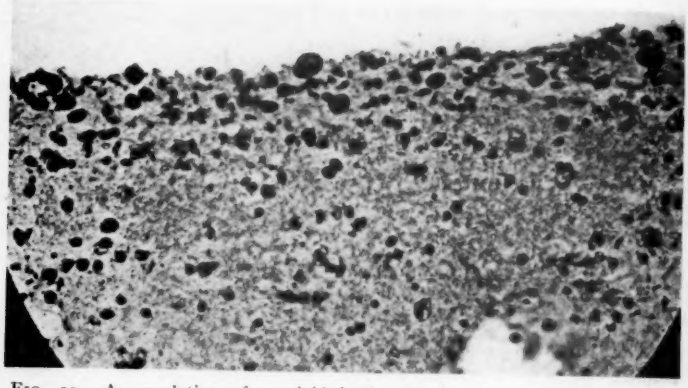

FIG. 10.—Accumulation of amyloid bodies in the Ammons horn. Globus-Penfield modification of Hortega method.

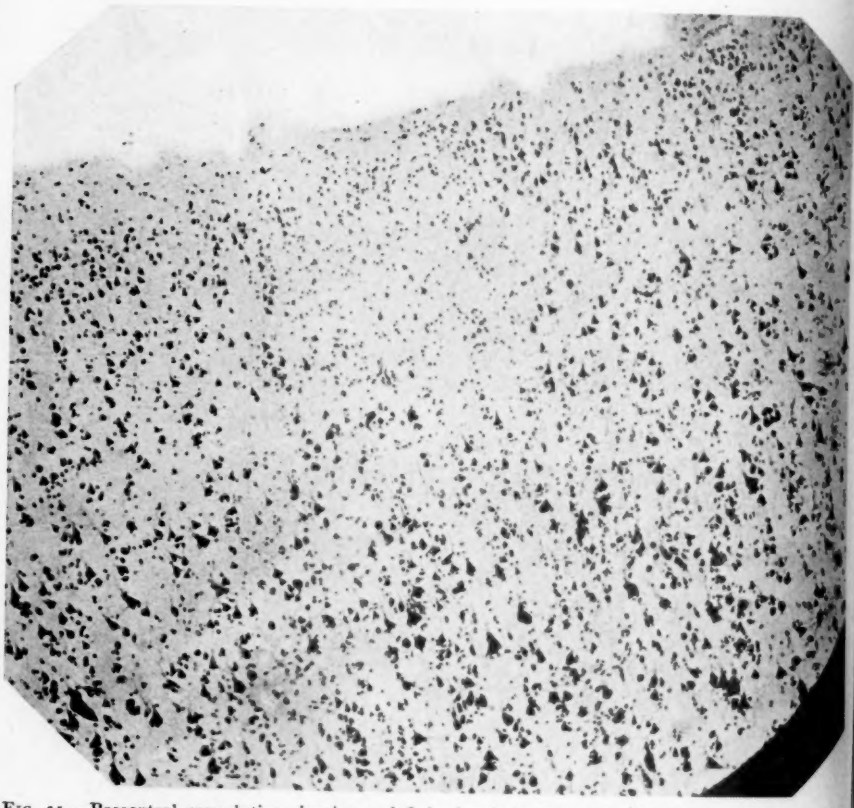

FIG. 11.—Precentral convolution showing a definite break in the continuity of the second and third layers due to disappearance of nerve cells. Nissl method.

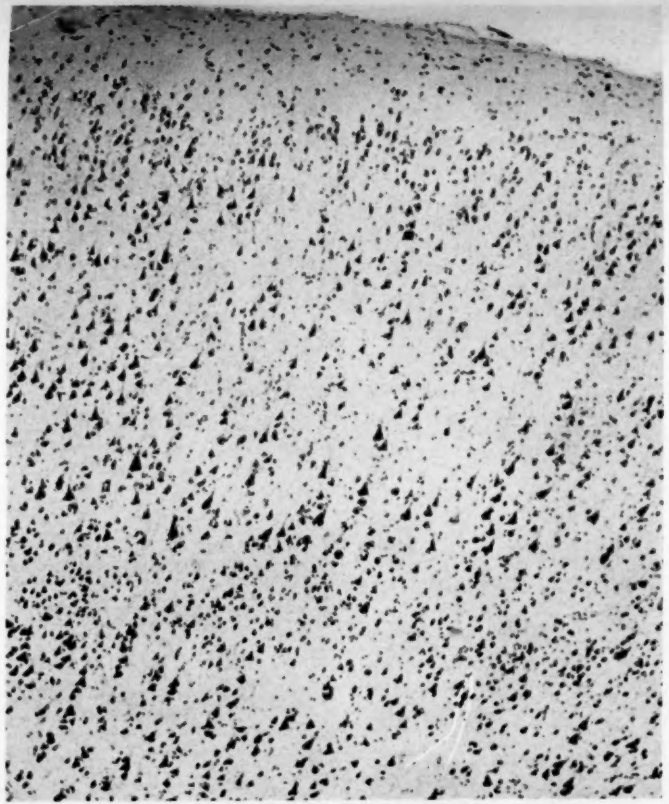

FIG. 12.—Third frontal convolution showing considerable disappearance of nerve cells, particularly in the third layer. Nissl method.

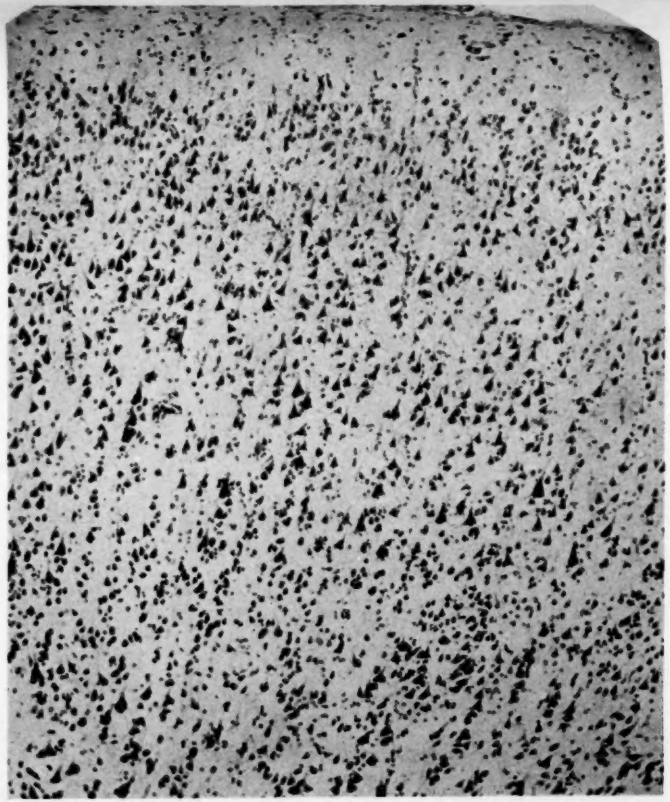

FIG. 13.—Third frontal convolution; normal tissue showing the considerable number of cells in the third layer to compare with the previous picture. Nissl method.

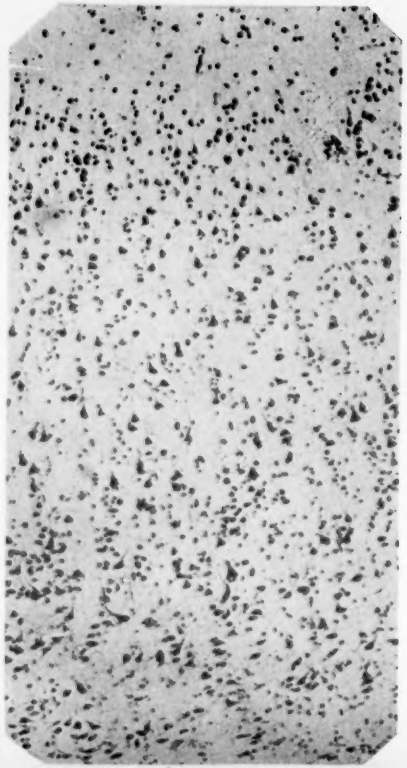

FIG. 14.—Second temporal convolution shows considerable disappearance of cells in the third layer. Nissl method.

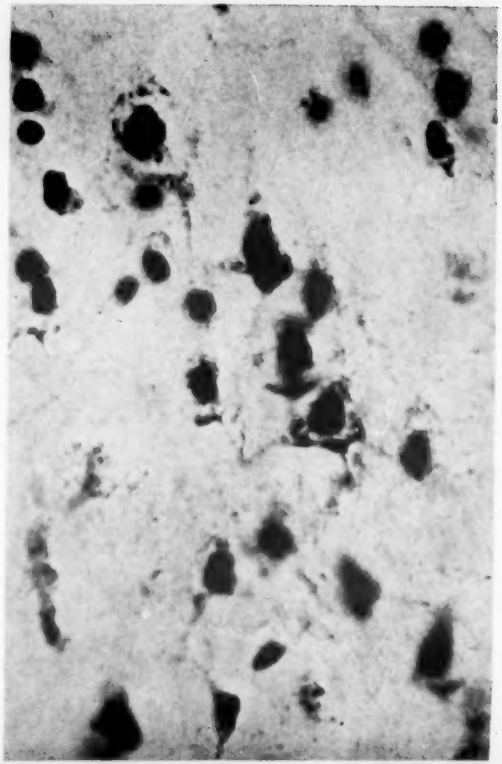

FIG. 15.—Second temporal convolution showing acute degenerative changes of nerve cells in the third layer. Nissl method.

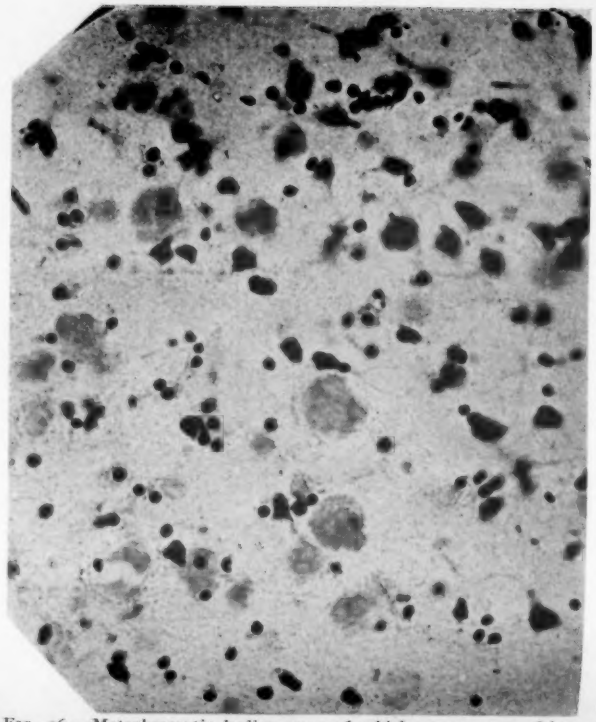

FIG. 16.—Metachromatic bodies some of which are seen resulting from degenerated cellular elements. Nissl method.

FIG. 14.—Second temporal convolution showa considerable disappearance of cells in the third layer. Nissl method.

FIG. 15.—Second temporal convolution showing acute degenerative changes of nerve cells in the third layer. Nissl method.

FIG. 16.—Metachromatic bodies some of which are seen resulting from degenerated cellular elements. Nissl method.

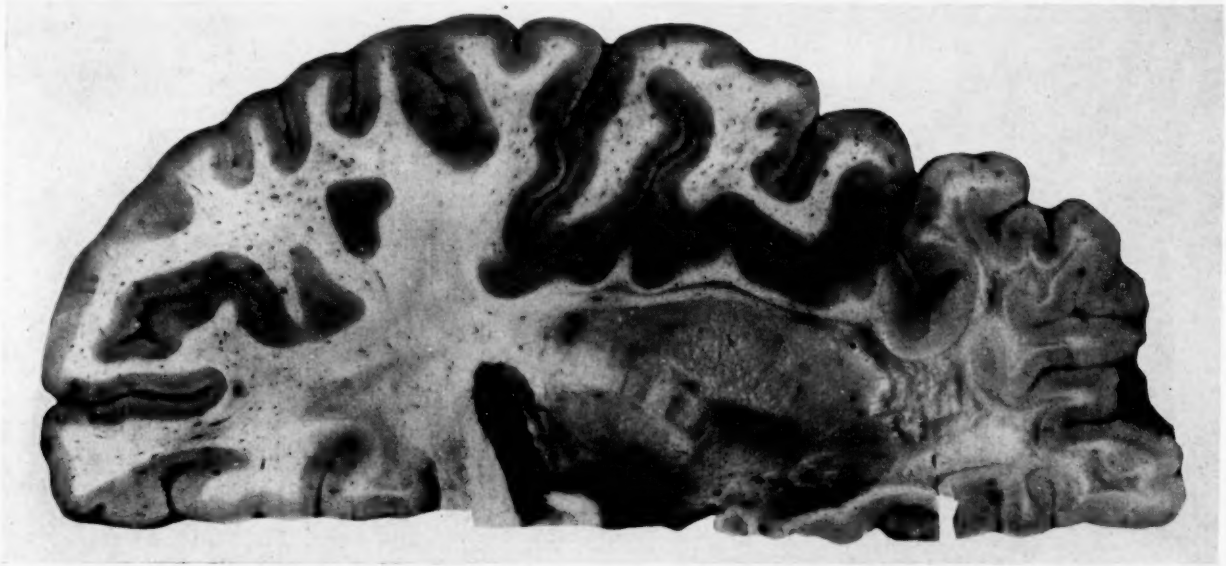

FIG. 17.—Horizontal section of brain showing the pathological process particularly pronounced in the frontal lobes.

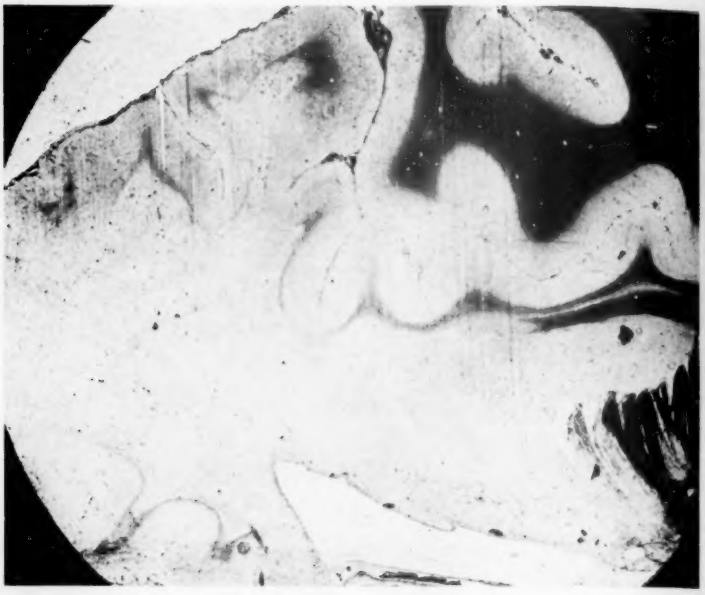

FIG. 18.—Horizontal section of the frontal pole showing complete demyelination. Weigert method for myelin sheaths.

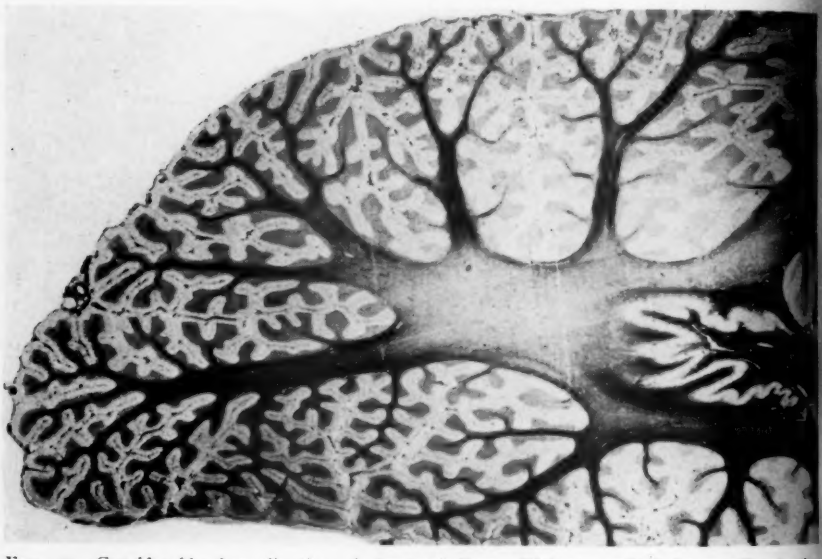

FIG. 19.—Considerable demyelination of the cerebellum. Weigert method for myelin sheaths.

FIG. 20.—Patchy areas of demyelination in the pons noticeable in both the right and left sides of the picture. Weigert method for myelin sheaths.

FIG. 21.—Details of the process of gliosis. Holzer method for glia fibrils.

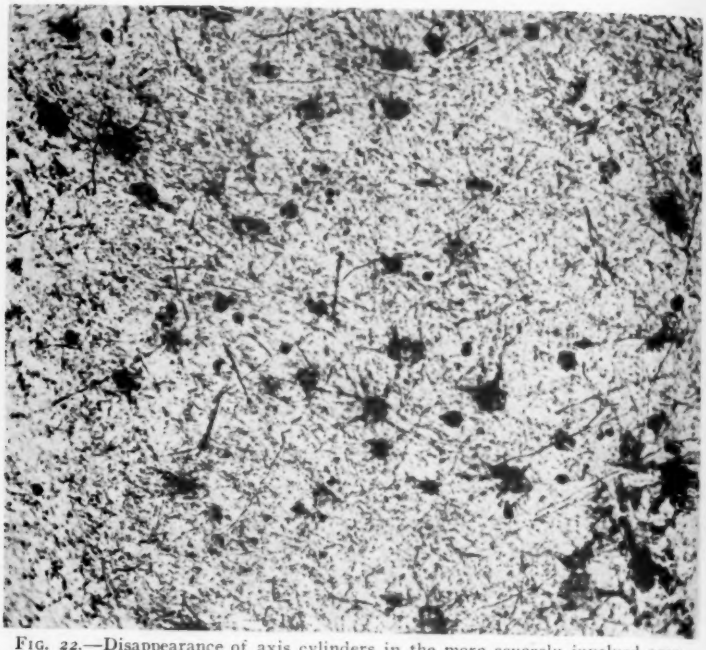

FIG. 22.—Disappearance of axis cylinders in the more severely involved area. Bielschowsky method for neurofibrils.

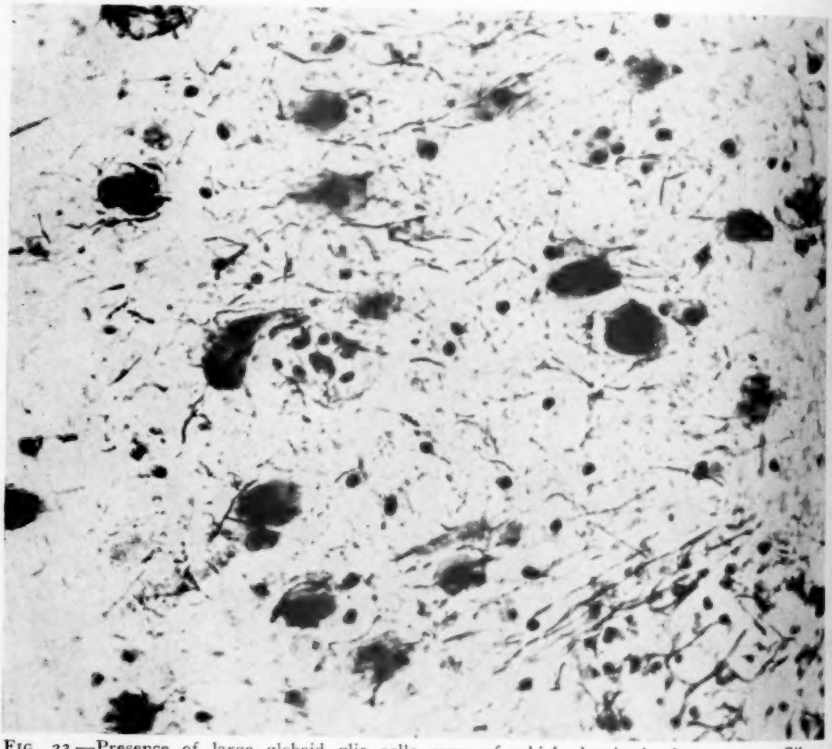

FIG. 23.—Presence of large globoid glia cells some of which deprived of processes. Silver impregnation method of Bielschowsky.

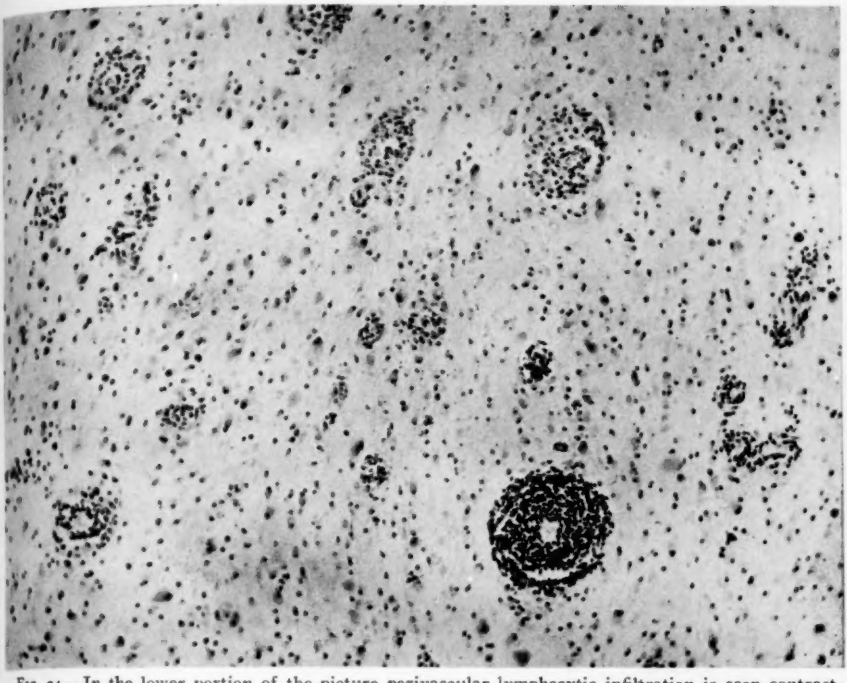

FIG. 24.—In the lower portion of the picture perivascular lymphocytic infiltration is seen contrasting with the perivascular accumulation of gitter cells in the remaining portion of the picture. Nissl method.

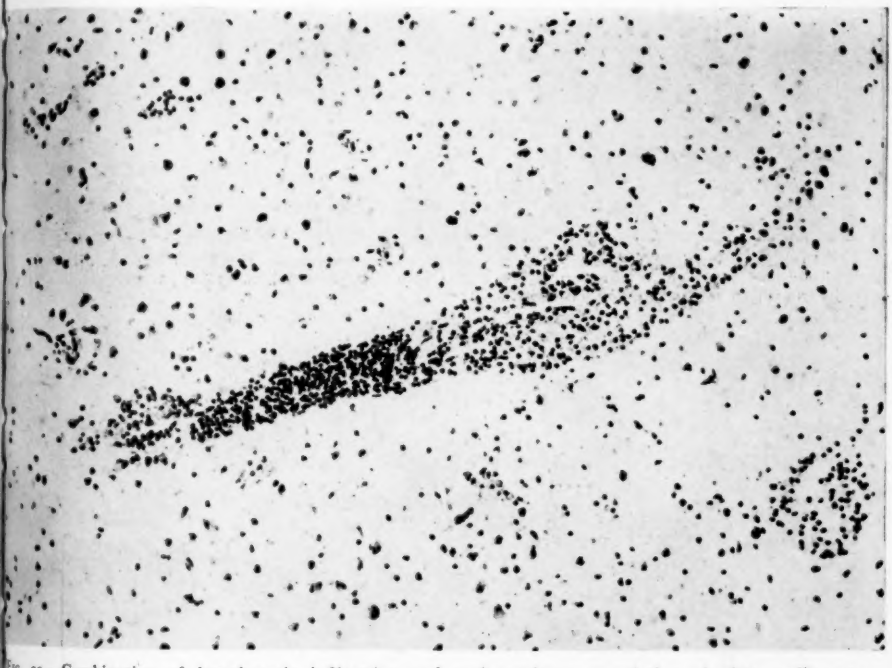

FIG. 25.—Combination of lymphocytic infiltration and perivascular accumulation of gitter cells surrounding the same group of blood vessels. Nissl method.

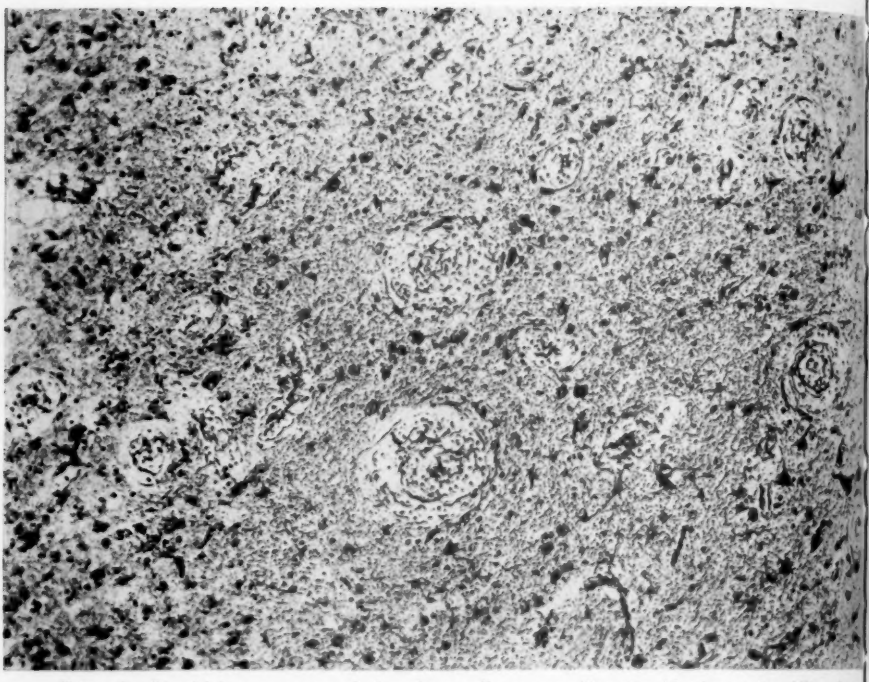

FIG. 26.—Syncitial appearance of the gitter cells surrounding the blood vessels. Note the absence of invasion of the connective tissue into the surrounding brain parenchyma. Silver impregnation method of Bielschowsky.

It is unfortunate that I had no opportunity to study the other organs of the same case in order to establish whether concomitantly with the brain lesions there was an involvement of important structures such as the liver, intestine and kidneys, the detoxifying function of which seems to be an accepted fact.

CASE 2.—J. A. R., a boy 14 years of age; admitted to the Buffalo State Hospital February 11, 1921.

Family History: Maternal grandfather's half-brother was insane and died at the age of 76. He was a cocaine addict; mental diagnosis, paranoid condition. Maternal grandfather's half-sister was insane for 17 years; in several institutions, and finally recovered. Paternal second cousin shot himself at the age of 16; the boy wished to learn a trade, but his parents having means and culture thought this beneath him. He was a truant from school for three weeks and the father was severe in his punishment. It is uncertain if the boy killed himself because he did not want to go to high school or from fear of punishment. A maternal uncle at the age of 15 refused to continue school after finishing his common school education. His teacher said he had lost interest and had become a dreamer. His wish to leave school was granted and now he holds a responsible position in a steel plant. The family is said to be intellectual, proud, religious, and many are holding positions of trust and responsibility in trade and profession. They are bright, strictly moral and self-respecting citizens.

Personal History: Was born in Buffalo, N. Y.; age 14. He was a full term child and delivery was normal and short. Infancy and early life uneventful. He began school at about the age of five and attended up to two years before admission, and advanced to the eighth grade. He was bright and learned readily. He had measles, mumps, whooping cough and chickenpox when a child; all were light and he suffered no complications. Had no accidents or operations. Total abstainer. He was of a sunny disposition, affectionate and cheerful, good natured and liked by every one. He did not let things bother him. Was impulsive and of rather irresponsible, indifferent nature. He soon forgot quarrels and punishments after promising to do better. He never held a grudge. He was accustomed to severe discipline and severe punishment. He played naturally with others, was a leader and got along well with most of the boys except one who also wanted to be a leader. He liked to read and had a vivid imagination. He was fond of the outdoors, but did not like swimming or baseball. He was always well behaved away from home and made friends easily. The home was comfortable and showed good taste and studied interest in the children for whom toys, books and magazines were provided.

Psychosis: Duration two years. He objected to school homework, saying it was too hard; failed in his examination in January, 1919, and felt discouraged. In March, 1919, he became truant. He would return home in the middle of school hours saying the school door was locked or else that he had returned to work in the garden. He would work for a short time and

then hike in the woods; corrected, he would run away and once remained away two days. He was expelled from school in January, 1920, the teacher stating he was not interested and troubled the other children when he did attend. He was home then until April, 1920, and "cut up" and "indulged in pranks." Finally his father, in April, 1920, applied to the Childrens' Court to see what could be done. Up to this time he had paid no attention to this opposite sex, but just before his commitment to a detention home he made an attempt to sexually assault his four year old sister. He was kept on probation for a short time and while on probation stole a bicycle, rode into the country and left it, walking home a distance of three or four miles. He gave no reason for stealing the bicycle, except that he wanted to take a ride. Became very untruthful and unreliable. He stole money from his parents. Once said he had been away with a tramp and wanted to go to Cleveland with him, but was refused passage on the steamship. He began to destroy things and seemed to have no sense of responsibiliity. Did things impulsively without sense or reason. On May 18, 1920, he was sent to the Berkshire Farm, a place for delinquent children, and remained there until July 12, 1920. He ran away from this school, nude, because the boys were pulling him by the legs and he said he was afraid. He was examined, considered unfit for the farm, and on July 12, 1920, was taken home. He was cared for by a neurologist who gave him "suprarenal gland treatment." He finally refused all treatments and began to run away again. He attended a home week celebration and it seemed the excitement upset him and he became unmanageable. In the latter part of August, 1920, he came downstairs, after going to bed, got the bread knife and ran out of doors saying he was looking for burglars who were trying to get in the house. Out of control, he was sent to the City Hospital in Buffalo, December 23, 1920, where his case was diagnosed "constitutional inferiority." He was sent to the Detention Home again and after a day or so committed to the House of Industry about September 18, 1920, where he remained until November 23, when he was sent to Randall's Island, N. Y., because of his behavior. He was immodest, masturbated, and exhibited sexual perversions. He was at Randall's Island until January 4, 1921, and there acted as he did at the House of Industry and they were unable to keep him. He was sent to Bellevue Hospital for observation, where he remained until January 24, 1921, when he was returned to Randall's Island with a diagnosis of being insane and it was recommended that he be sent to Buffalo and committed to the State Hospital. At the City Hospital he was destructive, irrelevant, and had auditory and visual hallucinations. He imagined that he saw burglars about.

Admitted: Buffalo State Hospital, February 11, 1921. Here he was quiet, agreeable and compliant, looked alert as if acquainting himself with his surroundings and was attentive when examined but careless, unreliable, untruthful and contradictory and all the time seemed amused in his attitude. He would answer a question or two but when censured would become flippant and answer haphazardly, occasionally adding some irrelevant remark with a silly explanation for it. Was shallow. Asked a question, he would

repeat it and then ask a question in answer. Said he heard voices telling him to steal automobiles and one day he was passing one and a husky voice said, "Take that automobile and go for a good time." Said he took the automobile and was taken into custody by the state police, and for this offense was sent to the Berkshire Industrial Farm (Not so) and that he stole another automobile and got as far as Hamburg when the gasoline gave out and he abandoned the machine (Not so, it was a bicycle). Thought he was sent to the City Hospital, Psychopathic Ward, for striking a cat with a big stick (Not so). He was untidy by wetting and soiling and masturbated without shame. Some of his answers to questions were: (How long have you been nervous?) "About a year." (In what way were you nervous?) "My fingers would jiggle." (What else?) "That is all." (Had any other trouble?) "No." (Why did they send you here?) "I guess I was too nervous around home." (In what way?) "I saw an automobile on the street and got nervous over that." (How did that make you nervous?) "Well, I guess I got into it and drove it away." (Steal it?) "Sure." (What did you do with it?) "Sold it for $500.00." (Not so) (What kind of a car was it?) "Rolls-Royce." (When did you leave the Berkshire Industrial Farm?) "About three months ago, fire insurance." (What do you mean by fire insurance?) "When a fire starts a building is insured isn't it." (But why did you mention it?) "I don't know." He spoke boastfully of being cruel to animals, as shooting a rabbit's leg off, killing them with a club, and cutting a pig's throat with a butcher knife, and it was "all for fun."

Orientation was correct in all fields excepting an error as to the day. Said he had not acquired the names of any one here. (What kind of patients are here?) "Crazy." (Are you crazy?) "No." (Why did they send you here?) "Being crazy." (Then you are crazy?) "Yes." (Which is right?) "I am crazy." (What makes you think so?) "My actions." (What were they?) "I would get a knife and try and cut my finger off." (What for?) "Just for fun." Memory for the recent and remote past seemed unimpaired but he continued careless and would not apply himself. After being censured his answers were better for a few questions. Retention good. He answered questions pertaining to school knowledge, etc., carelessly and made errors. Asked the Lord's Prayer, said, "Our father in Heaven, I thank thee for your kindness to them, wherever they sleep, wherever they bunk, wherever they sleep." (Who is president?) "Wilson" (Correct.) (Who was the first president?) "Wilson." (Who was the president before Wilson?) "Grover Cleveland." (When was the Civil War?) "1875." (When was the Spanish-American War?) "1767." (When did the last war end?) "1913." (How many inches in a yard?) "180, 72 inches in a foot, 3 feet in a yard." (When is Lincoln's Birthday?) "The 22nd of February." (Memorial Day?) "May 21." (When is Labor Day?) "October 2." "Misery" was where one cried and "poverty" where one got up and walked away with a thousand dollars. In calculating he was careless in doing the multiplication table and made errors. He read well but had to be prompted to

give the details. His writing showed nothing of special note. Asked questions pertaining to insight; he said he was crazy and showed indifference. Judgment obviously poor.

Physical Examination: Height 4 feet 11½ inches. Weight 102 pounds. Lymphnodes palpable in the groin. Genitals developed to adult size. Phimosis marked. Wassermann of blood serum negative.

Temperature, Pulse, Respiration: Normal.

Makeup and Appearance: Skull and face symmetrical. Ears normal. Nose straight. Teeth in good condition. Pivot tooth missing. Palate normal. Chin pointed. Complexion light. Hair dark and plentiful.

Scars and Bruises: Scars on right forearm result of itch a year ago.

Nutrition and Development: Well nourished and developed. Subcutaneous tissue of good amount. Muscles of good tone and size. Muscous membranes of good color. No chronic rheumatic condition. Thyroid not palpable.

Nervous System: No complaints. Vertigo, headache, neuralgia, pain paræsthesia denied.

Smell and Taste: Unimpaired

Eyes: Expression bright. Lids normal. Globes show nothing unusual. Conjunctivæ healthy. No nystagmus. No strabismus. Pupils regular, equal and react promptly to light and accommodation. Color sense good. No hemianopsia. No contraction of the visual field. Diplopia denied.

Ears: No complaints. Hears normally.

Cutaneous Sensibility: No subjective complaints; no tenderness of nerve trunks and muscles. Tactile sensibility, localization, pain, temperature, pressure, and stereognostic sense unimpaired.

Vasomotor and Trophic Changes: No salivation, seborrhœa, cyanosis, glossiness, loss of hair. No hair growth of chest and just beginning at pubes. No general or localized perspiring. Sergeant's white line marked. Only rough friction produced redness and that not very marked.

Motor Functions: Forehead can be wrinkled. Facial muscles and muscles of neck under control. Tongue protruded straight. Grips are equal and strong. Coordination good. Stands well in Romberg position. Gait normal. No clonus. No hypertonus. No tremor of protruded tongue and extended fingers. No fibrillary twitchings. Speech unimpaired.

Reflexes: Wrist present and equal. Patellæ normal and equal. Triceps seems more easily obtained on left side. Abdominal and plantar present.

Convulsions: Denied.

Thorax: No complaints. Normally developed. Good expansion.

Lungs: Examination negative.

Heart: Examination negative.

Blood Vessels: Superficial vessels not palpable. B. P. 95-78.

Digestive and Abdominal Organs: Tongue clear and moist. Appetite good. Bowels regular. Abdomen flat. Percussion and palpation of abdomen normal. Kidneys not palpable.

Genito-Urinary Organs: No history of syphilis or gonorrhœa. No scar present. Has pronounced phimosis. No discharge present.

Diagnosis: Dementia Præcox, Hebephrenic Form.

Progress Notes: There was no improvement in patient's mental condition following his admission to the hospital. He was careless and indifferent in his appearance and surroundings. He was so childish that the attendants spoke of him as feebleminded. He was unreliable, untruthful, and contradictory; answered questions in an offhand, careless manner and better answers were obtained when he was censured. He masturbated often and shamelessly; associated with other patients showing sexual tendencies, sat on their laps and stroked their faces and the like. Was always untidy, soiling and wetting both night and day. He defaced the ward, chewed rags and dirty towels. He exhibited no affection for his people when they came to see him and acted towards them the same as he did towards physicians in a careless, indifferent, disinterested way and all the time would stare and seem a little amused. He would poke fun at them and was profane and obscene. He was unsociable and had nothing to say to others. Was mischievous or malicious. Destroyed another patient's glasses and photographs in a room. Was at times noticed to laugh and talk to himself. He never appeared hallucinated but when asked about voices spoke of them as recorded in the initial examination.

On November 28, he developed a cough and a temperature of 104; P. 120; Resp. 24; condition: lobar pneumonia. His temperature continued high, toxemia marked, became stuporous, grew rapidly weaker and stimulation had no effect. On November 30, he had a general convulsion and died directly after it.

Cause of death—lobar pneumonia.

Following receipt of the brain for study at the Psychiatric Institute, further information was asked from the Buffalo State Hospital concerning the eventual presence of physical signs pointing to an organic condition. It was reported that there were no mental or physical manifestations to suggest an organic condition; and according to the physician in charge, who saw the patient daily, his condition was such that no one could think of any other diagnosis than dementia præcox.

Pathological Study: A rather large brain, weight 1430 grammes (1330 at autopsy), symmetrical, well fixed and without distortion. The convolutional pattern was rather simple and there was no thickening of the pia mater except in the region of a few pacchionian granulations on each side of the longitudinal fissure. The color of the convolutions was not unusual in any way. Practically all of them were rather large and plain; also rather tense and swollen looking; the secondary fissures were few.

The blood vessels looked thin and the veins contained only a moderate amount of blood, the fine cortical twigs were only moderately filled.

Basal Aspect: This appeared to be normal, although the pia of the cisterna and on the orbital convolutions was somewhat tougher than might be expected; it did not appear to be thickened. The circle of Willis was complete but the vessels composing it were unusually small; they were retracted and nearly empty, which would in part account for their being small.

The cerebellum was of good size and of normal appearance. The floor of the fourth ventricle was slightly uneven, but not distinctly granular. Consequently the external examination was essentially negative except for rather small blood vessels and slight toughness of the basal pia mater.

The brain was cut by removing the cerebellum and separating the cerebral hemispheres in the median line. The cut surfaces were not unusual in any way except that the genu of the corpus callosum had a somewhat gelatinoid appearance; it seemed slightly less firm than the rest of the callosum and instead of being white and opaque as elsewhere was decidedly translucent. The reduction in consistency was, however, not very marked. No granulations were seen in the third ventricle or aqueduct of Sylvius.

The pineal gland was large and contained four small cavities; it was only slightly gritty to touch.

Semi-horizontal section through the left hemisphere showed fixation in the basal nuclei and deep parts to be complete, but there was a peculiar appearance in the marrow underlying the whole prefrontal region as follows: instead of being white, as elsewhere, the marrow was grayish and translucent, but not uniform and homogeneous; it was instead somewhat mottled and curdy looking, with a very narrow white streak of normal looking marrow immediately adjacent to the gray of the cortex at all parts. This change stopped abruptly at the anterior border of the corpus striatum, but continued backwards along the claustrum and external capsule for a distance of about 12 mm. To touch, this gray subcortical tissue was not quite as firm as the normal looking marrow in other parts of the hemisphere. The marrow underlying the gyrus fornicatus showed the same grayish mottled translucent change.

After the brain had been examined for some time and had had a chance to drain and some evaporation of fluids had taken place, these translucent areas dropped below the general cut surface and though they still looked curdy there was a fine netted appearance in them as if they were traversed by fine strands of connective tissue (Fig. 17) in which the depressed and curdy appearance is brought out (especially just in front of the corpus striatum) but not the netted structure. The narrow stripe of preserved white matter immediately subjacent to the gray matter of the cortex is well shown.

Histological Study: The essential histopathological findings consist in a process of diffuse sclerosis which invades most of the white substance, though it is predominant in the frontal lobes. Here and there in the absence of diffuse sclerosis, patches of insular sclerosis are found in the most varied locations; and finally, transitional areas in which from small patches of sclerosis larger patches are formed through coalescence. The frontal pole which has the shrunken appearance already described, is the seat of an almost complete process of demyelination. Fig. 18 illustrates the severe process of demyelination detectable by the Weigert-Pal method. It can be seen that most of the white matter of the frontal pole has disappeared and that only some of the fibers forming the so-called " U " fibers contain a certain amount of myelin. A piece of the frontal convolution stained by the Spielmeyer method confirms the existence of a diffuse process of demyelination, with the exception of a certain amount of fibers of the " U " system arcuate fibers. More or less diffuse areas of demyelination are found in the occipital, parietal and temporal lobes, but not as pronounced as in the frontal. The cerebellum is also the seat of a considerable process of demyelination as seen in Fig. 19. Here also there seems to be a lesser involvement of the immediately subcortical fibers. In the pons (Fig. 20) the process of demyelination is not very diffuse, but is of the patchy type characteristic of multiple sclerosis.

Neuroglia: Corresponding to the areas of demyelination there is a considerable proliferation of neuroglia fibers which in places are enormously developed, the whole white matter being entirely occupied by a very rich and thick network of glia fibrils. The most intense gliosis is localized in the central portion of the white

matter, whereas the immediately subcortical layers have a less pronounced gliosis corresponding to a better preservation of myelin sheaths. Fig. 21 illustrates the details of the gliosis as detected by the Holzer method. In some areas the glia fibers are so thick as to lose considerably their individuality. In others, the glia fibrils are looser and better individualized.

Neurofibrils: With the Bielschowsky method for neurofibrils it is found that the nerve fibers have considerably suffered from the pathological process and that in the areas where the demyelination is complete and where the gliosis is very pronounced, the nerve fibers are practically absent though here and there axis cylinders are still evident, some of which are considerably fragmented.

In the areas where the involvement of the axis cylinders is not very severe, all phases of pathological reaction are noticeable ranging from the acute swelling to the rosary-bead appearance, fragmentation, and the complete disintegration of the nerve fibers. In some areas though the myelin sheaths have been considerably involved, the axis cylinders are much better preserved.

Fig. 22 illustrates the disappearance of nerve fibers as detected by the Bielschowsky stain. In the midst of the demyelinated area there are large cells which give the tissue a very characteristic appearance (Fig. 23). They are revealed by both impregnation and staining methods and represent large glia elements with considerable cytoplasm and nucleus generally displaced to the periphery. These elements are seen not only where the nerve fibers have entirely disappeared but also in areas with some preservation of nerve fibers and myelin sheaths.

The question arises here of the real nature of such large cells. I, personally, am inclined to feel that they are not elements performing exclusively a function of repair in the usual sense of the word. If this were the case, we would find them particularly in the areas of considerable demyelination, whereas we see them all over the white substance, a fact which points to the possible occurrence of hypertrophic changes of the glia cells independent of the process of repair. The contention that the glia elements play an important and possibly a primary rôle in the process of diffuse sclerosis has been advanced by other authors. Personally, I feel that the same agent responsible for the process of demyelination is responsible for the glia reaction in its particular aspect of

both hypertrophic and repair manifestations. The occurrence of such hypertrophic changes in glia elements as the result of the stimulus of a toxic or infectious agent opens our mind to the possibility that in other conditions where those same large cells are found in nests scattered here and there in the white matter as well as in the gray matter, they might also be the result of the toxic or infectious stimuli. I refer particularly to tuberous sclerosis in which large collections of such elements are found.

Gitter Cells: The white substance contains around the blood vessels a large number of gitter cells, elements derived from the transformation of microglia, oligodendroglia and cells of the blood vessel walls. These gitter cells or compound granular corpuscles form the bulk of the elements surrounding the blood vessels and which at low power might give the impression of a perivascular infiltration. A detailed study of the cells, however, discloses a reticular appearance and leaves no doubt as to their nature. In the midst of the areas where the gitter cells form the dominant elements, a few blood vessels here and there disclose the presence of a real perivascular infiltration in the sense of small round cells which have the morphological characteristics of lymphocytes (Fig. 24). Only rarely plasma cells are detected.

In some areas there is a mixture of lymphocytes and compound granular corpuscles. In other areas there seems even to be a definite separation, part of the blood vessels being surrounded by lymphocytes and others by accumulated gitter cells (Fig. 25).

It is important to note that there is no invasion of the surrounding brain tissue by the lymphocytic elements nor by the connective tissue of the blood vessel walls. As a matter of fact, the blood vessel walls form a very distinct network in which all the reticular cells are included, quite separated from the surrounding ectodermic portion (Fig. 26).

Nerve Cells: The most notable feature is the considerable reduction in the number of the nerve cells in the various layers though lamination is not very severely disturbed. Here and there all the phases of degenerative changes can be followed, particularly in the frontal cortex.

The fat products of degeneration are found accumulated in the gitter cells.

Altogether, in this case we are dealing with a diffuse pathological condition which can be surely labeled as a process of diffuse sclerosis, the histopathology of which is identical with other cases of the same nature already described in the literature and to which, in the last few years, Schilder has particularly called attention.

The question arises now of the nature of the pathological process which has resulted in diffuse sclerosis. The fact that a certain number of blood vessels disclose perivascular infiltration of lymphocytes may lead one to the belief that the process is an inflammatory one. The fact, however, that only the minority of the blood vessels is surrounded by lymphocytes, whereas the majority of the blood vessels disclose perivascular collections of compound granular corpuscles, throws very much doubt on the significance of the lymphocytic infiltration.

There are two possible explanations: first, that the process originally is an inflammatory one and that gradually the inflammatory reaction has disappeared being succeeded by perivascular accumulation of gitter cells. Against this conception is, however, the fact that should the process be originally an inflammatory one, we should find the predominating elements to be lymphocytes or we should at least find more often a mixture of lymphocytes and compound granular corpuscles. We also probably should find a spreading of the mesodermic tissue into the ectodermic tissue, a fact particularly reported in true inflammatory processes and which has not been noticed in the present case.

The other possible explanation is that the type of inflammation is what we would call reparative or symptomatic inflammation resulting from the large excess of products of disintegration to be taken care of. In support of this conception is the absence of inflammatory reactions in the meninges and in the cortex.

Comments.

It is natural that the question of diagnosis should be first taken into consideration. There is no doubt that a variety of opinions might be expressed regarding some mental conditions. The two cases which I have described were diagnosed clinically as dementia præcox. In the first one the diagnosis made by the examiner was confirmed by the staff conference. In the second case the diagnosis

was unquestionably one of dementia præcox and no signs pointing to an organic involvement of the brain could be detected during the stay of the patient in the state hospital and in the course of the numerous examinations there received.

In the first case, the histopathological study revealed the presence of an encephalopathy which bears the ear marks of a toxic process and which consists of patchy demyelination with replacement of the disintegrated tissue by proliferated glia fibers and concomitant involvement of the cellular elements of the cortex, particularly in the frontal, central and temporal areas.

In the second case the process was one of diffuse sclerosis and the pathology is a quite severe one, though unaccompanied clinically by neurological manifestations. The predominance of the lesions in the frontal lobes has been already emphasized.

We are, therefore, dealing with two cases in which the clinical manifestations have been those of dementia præcox, one of the catatonic type, the other of the hebephrenic type. In both cases a definite histopathological process has been found.

In the first case, the duration of the psychosis was very short, altogether 15 days, and correspondingly, the pathological process in the brain is also a recent and not very advanced one. In the second case the psychosis has lasted approximately two years and the pathological process points to such a long duration.

The reason for my illustrating these two cases is to call particularly the attention of the clinicians to the fact that cases of so-called functional psychoses exist in which the clinical manifestations of any organic component may be entirely lacking, and that such cases may nevertheless have as a basis a definite pathological process of the brain. I also wish to call attention to the fact that we cannot in the clinical diagnosis rely too much on the existence of the so-called organic type of reaction, as such organic type of reaction may be entirely absent clinically though a definite organic pathological process is present in the brain. It naturally follows that it is not safe to assume that at the basis of dementia præcox no organic disease may occasionally be found. The two cases here reported furnish evidence to the contrary. These cases also point to the necessity of broadening our conception of dementia præcox in the sense that we may not be dealing with a definite

disease entity, but presumably with a symptom complex group which can be generated by more than one pathogenic factor.

It is not the place here to enter into a discussion of the importance of psychological elements in the determination of such pathogenic factors, or of the possible interrelations between psychogenic elements and organic changes. It seems to me, however, in the light of the favorable personalities of the patients, that in these two cases psychogenic factors played no obvious rôle in the development of the acute mental condition.

I wish, therefore, to conclude that among the various pathogenic conditions which might result in a mental disease, the clinical manifestations of which may be labeled dementia præcox, we have to consider the possibility of definite organic changes and therefore be on the lookout, more so than in the past, for such an occurrence even in the absence of definite clinical organic symptoms. This ultimately means, to keep an open mind as to the possible organic nature of some functional psychoses which some psychiatrists tend too easily to label under one single group to which they deny any organic substratum.

DISCUSSION.

Dr. Lydia Baker Pierce (Westborough, Mass.).—I was keenly interested in these two cases presented by Dr. Ferraro, and I feel that they should stimulate us to make careful histopathological studies of all brains that come to us from the autopsy table.

Dr. Winkelman reported last year certain vascular changes associated with destruction of the ganglion cells, that he found in cases of dementia præcox. As long ago as 1901, when Dr. Adolf Meyer was working at the Worchester State Hospital, he reported from a series of 200 autopsies, eight cases which showed most interesting histopathological changes. These were not all dementia præcox. Some of them were senile psychoses. Several of them were patients who had shown an agitated depression. One was undoubtedly dementia præcox of the catatonic type with a duration of five months and death. These changes, you may remember, were most evident in the Betz cells which presented the axonal type of reaction. They were swollen, with eccentric displacement of their nuclei and chromatolysis. In some there was a whirlpool arrangement of the chromophil particles. Some of the other larger ganglion cells were also affected, in much the same way, I should say, as those Dr. Ferraro has shown us.

He also found destruction of the myelin sheaths of fibers in the white substance underlying the cortex.

We can't draw conclusions from a few cases, however interesting they may be. Certainly there are many of us who find it difficult to explain dementia præcox, with its terminal deterioration, on the basis of psychogenic factors alone. Whether, however, the organic changes observed from time to time can be attributed to the effect of the disease or whether they are the result of certain concomitant factors which may or may not be associated with the disease is a problem to be solved.

It is interesting that in both of the instances Dr. Ferraro has reported, the family history presented cases which clinically so closely resembled the patients described in this paper. It is a pity that the brains of these other psychotic members of both families could not be subjected to a careful study such as Dr. Ferraro has made of the material which he has reported.

Notes and Comment.

DR. MAY ELECTED MEMBER OF THE SOCIÉTÉ MÉDICO-PSYCHOLOGIQUE.—It is agreeable to record that at the meeting in Paris, November 27, 1933, M. Georges Dumas presiding, the Société Médico-Psychologique upon recommendation of a committee composed of MM. Pierre Janet, Capgras and René Charpentier, elected Dr. James Vance May of Boston *membre associé étranger* of the society.

This merited distinction comes to Dr. May following his presidency of The American Psychiatric Association, and his sponsoring in his presidential address the movement to raise psychiatric standards on this continent, with particular reference to the qualifications for membership in The American Psychiatric Association.

THE 1934 MEETING.—Very shortly the Preliminary Program of the 1934 Meeting of The American Psychiatric Association in New York will be sent to all members for their information. As noted in the previous announcement, the headquarters will be at the Waldorf-Astoria and members will find it an advantage to make reservations early. Parking arrangements are available in the immediate neighborhood of the hotel.

There are other hotels in the vicinity where reservations may be made for those who do not wish to stop at the headquarters hotel.

The usual arrangements are being made for transportation and there will be rates of a fare and one-third by using certificates, on all railroads. In some cases, especially Western railroads, where the tickets are bought on weekends, the rates will amount to slightly less. Further details will appear in the Preliminary Program.

The Association for Mental Defectives will meet, beginning May 25. The official date of The American Psychiatric Association is May 29 to June 1. There will be the usual overlapping in the meetings of the two Associations.

The Council has authorized both scientific and commercial exhibits. Those interested in contributing to these exhibits should communicate with Dr. Cheney, of the Committee of Arrangements in regard to the commercial exhibits and with Dr. Hamilton, of

the Program Committee with respect to scientific exhibits. Dr. Hamilton will be interested in learning of any films which might be available, showing mental hospital or related activities. The Program Committee has almost completed a well-balanced program. If any members have papers which they would like to have considered for presentation, they should communicate at once with Dr. Samuel W. Hamilton, Chairman of the Program Committee, Bloomingdale Hospital, White Plains, New York.

WORK OF THE ROCKEFELLER FOUNDATION.—The report for 1932 recently issued indicates the scope of the Foundation's activities in the fields of the medical, social, and natural sciences, the humanities, and public health. To cover these projects a total of $11,577,064 was appropriated during the year.

In the Division of the Medical Sciences, under the directorship of Dr. Alan Gregg, emphasis was shifted in recent years from building projects and medical school endowments to specific research programs. In 1932 special attention was given to neurology and psychiatry. The largest appropriation, $1,282,652, went to McGill University in Montreal for the establishment of a Neurological Institute. The departments endowed by this appropriation include laboratories, clinical neurology, neurosurgery, neurophysiology and neuropathology.

Appropriations for neurological research were also made to the Kaiser Wilhelm Institute for Brain Research in Berlin and to the Institute for Psychiatric Research in Munich for the study of infections of the central nervous system; to the Institute of Physiology of the University of Bern for investigation of the excitation processes in nerves; and to the London Hospital for training in neurosurgery.

Other projects in the medical sciences supported by the Foundation were studies of the physiology of the acoustic nerve at the Johns Hopkins Medical School; studies of whooping cough at Western Reserve Medical School; of virus diseases of the nervous system at both Columbia and Washington Universities; biological studies at the University of Paris Radium Institute; and research in sex problems by the special committee of the National Research Council.

During the year 383 fellowships were awarded for the training of research workers in the medical sciences.

Association and Hospital Notes and News.

CENTRAL MALARIA LIBRARY.—A malaria library was founded in Rome by the Stazione Sperimentale per la Lotta Antimalarica in 1925, and an "Index to Malaria Literature" is issued annually by the station.

To make this as complete a central malaria library as possible we appeal to all malariologists to send us books, reports and articles on malaria.

Photostat copies of any articles in the library can be had, on request at cost production.

All publications and requests should be addressed to "The Director, Stazione Sperimentale per la Lotta Antimalarica, Corso Vittorio Emanuele 168, Rome (16)."

NEW FEDERAL HOSPITAL FOR DEFECTIVE DELINQUENTS.—The United States Hospital for Defective Delinquents, located at Springfield, Mo., and authorized by the Act of May 13, 1930, was opened for the reception of patients on September 1, 1933. As an institution it occupies a significant place in the evolution of public policies in the treatment and amelioration of disease and illness, and also in the development of a coordinate system of correctional procedure. It was designed primarily for the care and treatment of the sick who have committed offenses against the United States, including those who are mentally ill and those who are afflicted with chronic and protracted physical disease. Specially designed facilities are contemplated for the tuberculous.

There is more in the conception of this hospital than the mere housing or domiciliary care of prisoners. It represents a medical center with all those diversified facilities which the broad activities and interest in modern medical science and the treatment of the sick entails. It represents even more than individual services for those admitted, for it is an aspect of specialization aiming at the solution of a special social problem confronting organized society. The rôle this institution occupies in the scheme of our social order

has behind it a continuous evolutionary growth of more than three centuries, until there has gradually come a realization that physical and mental defects and physical and mental diseases are complicating factors in crime and in correctional procedure. It is this realization that led to setting up the special facilities at Springfield. They have for their object the safety and protection of civil communities; the application of rehabilitation measures in existing correctional institutions uncomplicated by the presence of these special medical problems; the humane care, cure or amelioration of adverse physical states; and scientific studies for contributing to the sum of our knowledge concerning physical and mental disease and defect as motivating factors in crime, and the application of these results to future policies which a social order may adopt in meeting this special phase of the crime problem.

The opening of this institution represents a significant change in Federal approach to the crime situation. Moreover, the institution represents one of the coordinate units of the Department of Justice scheme of correctional procedure. The medical, technical, and scientific services are supervised and furnished by the United States Public Health Service. Fellow Lawrence Kolb of the United States Public Health Service is its first superintendent and chief medical officer.

THOMAS W. SALMON MEMORIAL LECTURES.—The New York Academy of Medicine has announced that Dr. Charles Macfie Campbell, professor of psychiatry at the Harvard Medical School and director of the Boston Psychopathic Hospital, has been chosen to deliver the 1934 series of the Thomas W. Salmon Memorial Lectures. Dr. Campbell's subject will be: "Trends in Psychiatry"; and the dates of the lectures are April 13, 20 and 27.

At the January meeting of the Academy when this announcement was made a portrait of Dr. Salmon was presented to the Academy by the Thomas W. Salmon Memorial Committee. The presentation was made by Dr. C. C. Burlingame, physician-in-chief of the Hartford Retreat, chairman of the committee.

REPORT OF THE COMMITTEE ON THE SURVEY OF STATE MENTAL HOSPITALS OF PENNSYLVANIA.—A committee, composed of Everett S. Elwood, Esq., director National Board of Medical Ex-

aminers, chairman, and Drs. J. Allen Jackson, superintendent Danville State Hospital, Henry I. Klopp, superintendent Allentown State Hospital, William C. Sandy, director Bureau of Mental Health in the Pennsylvania Department of Welfare, recently studied the State Mental Hospitals of Pennsylvania and submitted a report to Governor Pinchot. This report is especially opportune at a time when most if not all hospital systems are having difficulty in maintaining existing standards because of budget limitations and decreasing revenues.

In a discussion of the evolution of humane care of the insane in Pennsylvania, Benjamin Franklin is credited with securing the initial appropriation from the General Assembly in 1751 for the establishment of the Pennsylvania Hospital at Philadelphia, with a provision that it contain a department for the reception and care of "lunatiks." In 1851 through the activities of Dorothea L. Dix the first State Asylum in Pennsylvania was established at Harrisburg. The first out-patient clinic for nervous diseases in the United States was opened in Philadelphia in 1869 at the Orthopedic Hospital and Infirmary for Nervous Diseases.

The later developments in Pennsylvania as elsewhere have been irregular. A dual state and county care system has continued with great variation in the quality of treatment throughout the commonwealth. Complete state care is the objective and this is gradually being approached but about half of the patients are still in county institutions.

With the establishment of the Department of Welfare and its Bureau of Mental Health in 1921, the activities in behalf of mental patients have been coordinated and inspirational leadership has been provided. A ten-year program of progressive development has been carefully planned and adopted. The state owned mental hospitals have become treatment centres with responsibilities for the development of constructive activities for the promotion of mental health in their respective districts, including such important preventive projects as mental clinics.

In the second division of the report are discussed the essentials of a modern mental hospital based upon the Ten-Year Building Program of the Welfare Department and the recommendations of The American Psychiatric Association. Detailed suggestions

are made as to the building essentials of a modern mental hospital and the personnel requirements for a 2000 bed hospital.

The committee in its final summary, stressed the desirability for complete state care; the necessity for maintaining present standards; the need for scientific study and treatment of patients; the importance of a study of the dietetic problems; the responsibility of hospitals as training and teaching centres; the necessity for extra-hospital activities including social service and mental clinics; and the desirability for a state psychiatric hospital as a centre for research, education of physicians and other personnel, such as the one planned in connection with the University of Pittsburgh, with a second in Philadelphia when this becomes possible.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION MEETING.—The eleventh annual meeting of the American Orthopsychiatric Association will be held at the Palmer House in Chicago, Illinois, February 22, 23, 24, 1934. Dr. Phyllis Bartelme is chairman of arrangements.

Book Reviews.

SCHIZOFRENIE. Bollettino Trimestrale del Primo. Centro Provinciale di Studio Della Demenza Precoce. Editoriale Scientifico-Practico dell-'Ospedale Psichiatrico della Provincia di Cuneo in Racconigi. Anno II, Vol. I, N. 2, June, 1932; Anno II, Vol. 1, N. 4, Dicembre, 1932.

In this Trimestral Bulletin devoted to studies related to schizophrenia and which is edited by the Psychiatric Hospital of the Province of Cuneo, in Italy, fasicule 2 contains several interesting contributions, particularly concerning the organic approach to dementia præcox.

Among the various contributions the one concerning the somatic constitution of the schizophrenia, by A. Vanelli, is of outstanding interest. The author, basing his study on 315 schizophrenics in which the constitutional type has been drawn according to the methods of Viola and Viola-Fici, concludes by pointing out the preponderance of the brachitype in paranoids and paraphrenics, whereas, the longitype predominates in hebephrenics and catatonics. An attempt by C. Roncati is next found concerning the clinical aspect of what he proposes to call the paranoid psychoses. These paranoid psychoses are represented by schizophrenics in which delusional ideas, hallucinations, and at times sub-confusional states develop for various and as yet non-definite causes. Such cases have generally a brief course and are of a favorable prognosis.

A contribution of A. E. Rizzatti and V. Martinengo is to the effect that according to the cytological study of the blood in 100 cases of schizophrenia the authors are willing to accept characteristic cytology of the blood in initial stages of schizophrenia, particularly in the hebephreno-catatonic types. The cytology consists in a slight leucocytosis with neutropenia, monocytosis, and lymphocytosis which they correlated to a possible toxic infective process.

An interesting contribution from the biochemical standpoint is the one of A. Chiabov dealing with the elimination of the neutral sulphur in urine of mental cases and concluding that in schizophrenia there are comparatively more abnormal values than in manic-depressive conditions.

The last paper of the issue deals with an investigation by G. Croce, on the incidence of tuberculosis and schizophrenia from the radiographic standpoint. It is concluded that in the hebephreno-catatonic and paranoid patients such incidence is generally very high. The tubercular infection is also present in initial cases of schizophrenia at a period when the development of tuberculosis cannot be related to unsanitary surroundings or long periods of confinement in hospitals.

In fasicule 4 of Vol. 1, an article by C. Pero relates the histopathological findings in the central nervous system following experimental intoxication with bulbocapnine. The study concludes that following such experimental

intoxication in cats, dogs, and rabbits the most common histopathological changes are the vacuolar degeneration, the fading of the nerve cells, and the grape-like areas of disintegration (Buscaino). The lesions are diffused all over the central nervous system but more so in the cortex and basal ganglia and such lesions resemble the lesions reported by various authors in cases of acute dementia præcox.

In three cases of schizophrenia, in which the constitutional elements of a Basedow disease were concomitant, G. Bianchi establishes a certain link between the glandular condition and schizophrenia in as much as the treatment for the Basedow condition determined also an improvement in the mental condition of the patient.

In a pharmacological exploration of the sympathetic nervous system in schizophrenia by A. Vanelle, the author concludes a survey of 300 schizophrenics investigated by the method of Danielopulo, by emphasizing the large incidence of hypoanfotonia in his cases, that is a condition of hypofunction of both the sympathetic and parasympathetic nervous systems.

In a contribution dealing also with the hematology of schizophrenia, V. Debeus reports his findings in 62 schizophrenics and 31 manic-depressives and concludes that in schizophrenia (hebephrenics and catatonics) there is a deviation of the blood formula towards the left with neutropenia, slight lymphocytosis, and evident monocytosis. In paranoids the deviation of the formula is less pronounced and so is the monocytosis. Conversely, in manic-depressives there is a lymphocytosis, eosinophilia, and shifting of the formula towards the right.

The issue is closed by the report of M. S. Levi on the functioning of the reticulo-endothelial system in relation to the absorption of red congo. The author establishes the fact that in almost all the schizophrenics there is a diminished functioning of the reticulo-endothelial system in regard to the red congo (method of Adler and Reimann) and therefore tries to establish the correlation between the diminished functioning of the reticulo-endothelial system and the presence of circulating toxic substances as a possible causative factor for the mental manifestations.

A. Ferraro,
New York.

Les Fonctions Sexuelles Males et Leurs Troubles. By *Stanislas Higier.* Preface du Professeur Laignel-Lavastine. (Paris, G. Doin and Co.)

In his book the author discusses the subject of the male sexual processes, both normal and pathological—(1) from the physiological, and (2) psychological point of view. He speaks to the urologist and neurologist in the physiological discussion of his subject, and to the psychiatrist and psychoanalyst when he attempts psychological explanations for various phases of the male sex status. There is no pretense at treatment, but the book is a physiological and psychological analysis of the normal and abnormal phases of the sex functions. The sympathetic nervous system is given a prominent part; not content with various physiological explanations, the

author follows the method of Havelock Ellis, with analysis and subdivision of such subjects as sexual impulse, pleasure, orgasm, etc. The book is valuable for its details, and for the amount and extent of material discussed in a single volume. It has been a long time since such a stupendous task has been attempted single-handed. By bringing the subject of normal and abnormal sex processes up-to-date, the author has accomplished an important piece of work. The book is recommended to every individual interested in sexology, as well as to specialists.

CHAS. S. LEVY.

THE MANIC-DEPRESSIVE PSYCHOSIS. By *Helge Lundholm, Ph. D.*, Associate Professor of Psychology, Duke University. Duke University Psychological Monographs Number 1. (Durham, N. C,: Duke University Press, 1931.)

This book should be in the hands of all psychiatrists as well as psychologists. The theory propounded is that the manic-depressive psychosis has a toxic basis, a theory that has had numerous advocates in the past. The author points out that this condition is allied to states brought on by depressant drugs and that there is a psychological basis for the belief in its toxic cause even though bio-chemistry has not satisfactorily proved it to be so.

Two premises are offered in the first chapter on "Formulation of the Problem and Outline of the Survey." These are: (1) "The gradual acquisition during mental growth, of adaptive integration of our cognitive-conative propensities into personality is probably concomitant, on the physical plane, to the gradual acquisition of integrative communications between the neurones and the neurone systems on the higher level of the nervous system, especially in the cortical." The second premise is: "The influence of a depressant drug on the nervous system is essentially to disturb or derange, in a general way, this neural integration of the higher brain-level, so as to produce, psychologically, exactly the state of general disintegration of personality."

In the second chapter, "The Adaptive Integration of Mind by the Processes of Sublimation and Repression," the author says: "The discussion of sublimation and repression which I have submitted here may seem rather speculative. It should be kept in mind, however, that the two concepts are hypothetical and that their only criterion of validity and realness is the pragmatic one of their usefulness in the explanation and organization of human experience." It would seem that this is too modest a statement.

The third chapter is entitled "Manic-Depressive Symptoms Directly Referable to a General Disintegrative Process." In this the author advances quite convincingly proof for the premises above stated.

"The Three 'Imperial Moods' of the Manic-Depressive Psychosis" is the title of chapter IV, and these are stated to be the feeling of unreality, the feeling of omnipotency, and the feeling of inadequacy. Here again the author would seem to prove his thesis.

Chapter V, "A Diagrammatic Summary of the Principles and Symptoms of the Manic-Depressive Psychosis," appears unnecessary and adds nothing to the foregoing. The last chapter entitled "General Theoretical Considerations" is a brief summary occupying but a single page.

The author is to be congratulated upon his clear presentation.

W. R. D.

INSOMNIA. HOW TO COMBAT IT. By *Joseph Collins, M. D.* Appleton Popular Health Series. (New York and London: D. Appleton and Company, 1930.)

This little book aims to furnish information of the causes and phenomena of sleep, the things that most frequently disorder it and where and how it is most readily and successfully reconditioned. These are presented in the author's interesting way and doubtless the book will be helpful to those who are troubled with poor sleeping habits. It will probably save the busy physician many hours of questioning and explanation if it is placed in the hands of such patients. It emphatically states that "the cultivation of an effective will is the most important step toward relief," a statement with which the majority of psychiatrists will probably agree.

W. R. D.

PREVENTIVE MANAGEMENT: MENTAL HYGIENE IN INDUSTRY. Edited By *Henry B. Elkind, M. D.* (New York: B. D. Forbes, 1931.)

This volume of 227 pages comprises a collection of eight papers, by outstanding workers, on the subject of mental hygiene aspects of industrial management. It is written for the average business executive and is based upon material originally presented in a course of lectures given in 1930, under the sponsorship of the Division of University Extension of the State (Mass.) Department of Education, in cooperation with the Massachusetts Society for Mental Hygiene.

This symposium covers the broad field of personnel problems in industrial relations. It is couched in simple, direct and untechnical terms which should make it not only interesting and readily understandable, but essential to the intelligent and progressive executive. An especially valuable and balancing feature also, is the fact that the roster of contributors includes not only psychiatrists but industrial engineers and lay personnel experts. The book contains helpful biographic notes preceding each essay and ends with a serviceable index and an excellent supplementary reading list.

To those particularly interested in this field, a somewhat more specific impression of the scope and nature of the work may be afforded through the appended full list of titles and authors.

Foreword—Henry Kendall.

I. Preventive Management: The Next Step in Industrial Relations—Meyer Bloomfield.

II. Human Nature and Management—Ordway Tead.

III. Psychiatry in Industry—V. V. Anderson, M. D.

IV. Practical Applications of Mental Hygiene in Industry—Henry B. Elkind, M. D.
V. Mental Pitfalls of Leadership—Harlow S. Person.
VI. The Industrial Aspects of Morbid Emotion and Fatigue—Karl M. Bowman, M. D.
VII. Fear and Nervous Energy—Abraham Myerson, M. D.
VIII. The Minor Executive and Mental Hygiene—Elliot Dunlap Smith.

THEOPHILE RAPHAEL.

LE DÉVELOPPEMENT MENTAL ET L'INTELLIGENCE By *Henri Piéron.* (Paris: Felix Alcan, 1929.)

This very interesting little book devoted to mental development and intelligence comprises four lectures given by Prof. Piéron at the University of Barcelona in 1926. The titles of the four chapters will indicate its scope: (1) Mental development and its stages; (2) The measurement of the levels of development; (3) Development and intelligence. Level and mental profile; (4) Problem in the evaluation of intelligence. Necessity of an analytical evaluation.

The book is broad in its scope, with many references to contemporary work, much of which is American, and there is a refreshing attitude to the limitations of the present day methods as well as to their usefulness. The portion dealing with the mental profile, quoting Rossolimo, Lasoursky and Vermeylen is of special significance to those interested in mental hygiene and the more theoretical notions concerning types of intelligence.

ESTHER L. RICHARDS.

THE INTELLIGENCE OF THE PROSPECTIVE IMMIGRANT. Public Health Bulletin No. 206. By *J. D. Reichard,* Surgeon, United States Public Health Service. (Washington: U. S. Government Printing Office, 1933. 5c.)

This bulletin presents the results of a study of mental ability measured by "language" and "non-language" tests of approximately 500 persons applying for American immigration visas at Warsaw, Poland. In general the results are presented in the form of two schedules; *i. e.,* non-language and language. The results of applying performance tests alone compare favorably with that seen in American school children over 10 years of age. Language tests, however, gave results below that of American school children over 10 years of age, in some language tests the results being strikingly lower.

Sex, schooling and age were significant factors influencing ability, whereas, only slight differences were associated with race. Non-language tests show the greatest differences in association with sex, and language tests with schooling. The most consistent variation in results was associated with age, the older age groups uniformly making the poorest showing.

The study is of value to all those agencies, both institutional and communal, that deal with the mental health problems associated with European immigrations.

J. D. REICHARD.

MALARIA TREATMENT OF PARENCHYMATOUS SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. Supplement No. 107 to Public Health Reports. By *R. A. Vonderlehr,* Past Assistant Surgeon, United States Public Health Service. (Government Printing Office, Washington, 1933.)

The favorable results obtained by the induction of malaria fever in the treatment of syphilis, and particularly syphilis of the central nervous system, make this paper of interest. The clinical results obtained in the treatment of parenchymatous neurosyphilis in 8038 cases are noted by years. A summarization of these results shows that 26 per cent of the cases were able to resume their former occupation, 22.3 per cent were improved, 28.3 per cent were unimproved and 23.4 per cent had died since the induction of the malaria. The communicability of induced malaria to the general population is an important public health problem and is considered in some detail. The histologic changes in the central nervous system and various theories as to the mode of action of the plasmodial disease upon syphilis of the central nervous system are considered. The technic of malaria inoculation as well as the treatment of the induced malaria are taken up. Brief consideration is also given to the question of prognosis. Contraindications to the induction of malaria which have been noted by a number of writers are described; those most commonly mentioned are cachexia, severe organic heart disease, tuberculosis, and nephritis, and other less common contraindications are listed. Serological changes taking place in the spinal fluid are described in some detail and various administrative and sociologic problems are discussed. The complications and sequelæ of malaria therapy are also described.

In addition to the treatment of parenchymatous syphilis, consideration is also given to the subject of prophylactic action of malaria in the prevention of the development of syphilis of the central nervous system and to the treatment of other forms of syphilis. A complete biblography through the year 1931 is appended.

W. L. T.

MENTAL DEFICIENCY DUE TO BIRTH INJURY. By *Edgar A. Doll, Ph. D., Winthrop M. Phelps, M. D.,* and *Ruth Taylor Melcher, M. A.* (New York: MacMillan Co., 1932.)

The problem which primarily attracted the attention of the authors was that of measuring the effects of physical therapy in cases of mental deficiency due to birth injury. Increasingly recognized in the medical literature during the past century for its physical and mental effects, birth injury has had very little attention as a specific problem in mental deficiency. The authors therefore propose to describe birth injury as a clinical category of mental deficiency by enumerating its mental and physical characteristics. A second purpose of their study is to point out the inadequacy of present psychological tests in evaluating the ability of individuals with motor and language handicaps, and "to suggest modifications which will give more satisfactory indications of their actual ability." Finally, they propose to use these methods to observe the effects on mental development of motor development resulting from physical therapy.

The effects of birth injury are, on the physical side, mainly spastic paralysis and athetosis, and on the mental side, amentia and personality deviations. Determination of etiology must be by a combination of history and neurological findings. Incomplete information makes it difficult to determine the frequency of occurrence of birth injury but it is probably more frequent than heretofore realized. It may affect mental development without showing such symptoms as would enable detection, thus simulating primary amentia. It may cause personality deviations such as irritability and distractability. It is possible that hydrocephalus and secondary epilepsy are occasionally due to birth injury. When motor effects are present the question arises as to whether the mental defect is directly due to injury or to the restrictions imposed on mental development by the motor incapacity.

The particular interest of this study is in cases showing both mental defect and motor impairment. The subjects were selected on the basis of: (1) Neurological diagnosis of cerebral lesion; (2) Present symptoms; (3) Family history (hereditary defect did not rule a child out); (4) Birth history (as information in this respect was incomplete it was not given a determining weight); and (5) Developmental history (in this the absence of childhood diseases was considered important in addition to early retardation). The cases were divided into two groups as follows: (1) A group of 7 cases with a history of birth injury uncomplicated by other factors. (2) A group of 5 cases with the complication of a neuropathic taint or a post-natal illness. The cases are described individually.

All cases showed some irregularity of birth, "difficult labor" being the most frequent. In all cases where they were recorded there was retardation in holding up the head (6 cases), in walking (11 cases), and in talking, (all 12 cases). In all cases but one there was a speech defect. It is noted that the degree of brightness bears no relation to motor development in these cases.

It is difficult to determine the mental status of the birth-injured. The authors point out that what is for the normal a test of general intelligence, may be a test of special aptitude for those handicapped in means of expression, as are the birth-injured. An attempt is made to evaluate several well known psychological tests as measures of the abilities of the birth-injured. The Stanford-Binet test receives the most detailed consideration. An interesting analysis of this test is made in which each item is compared as to its relative difficulty for three groups; (1) the group of birth-injured subjects; (2) a group of ordinary feeble-minded subjects paired as to sex, life age, and mental age; and (3) normal subjects as represented by the Stanford-Binet norms. On the basis the number passing each item the order of difficulty of the items is found for each of the feeble-minded groups—the birth-injured and the ordinary feeble-minded. Some interesting and surprising differences in difficulty are brought out by this method. A further step, however, is taken in the analysis which appears to be very questionable. All the items which prove to be of equal difficulty for one group are assigned a common mental age value for that group. This assigned mental age value is the average of the normal mental age values of the items in

question. But as the object of the comparison is to find the difference in difficulty of the items for the two groups, it appears unjustifiable to use the normal mental age values as a determining factor in the assigned value for these groups which differ from the normal in precisely this thing—the mental age value of a given item. More direct and reliable means are available for finding the relative difficulty. The authors are careful to point out the limitations set to their conclusions by an extremely small number of cases. Nevertheless the interesting differences in difficulty are strongly suggestive and warrant the checking of these results with larger groups.

The other tests used were the "Myers' Mental Measure," the Goodenough Drawing Test, the Healy Pictorial 1 and 2, the Porteus Maze Test, the Witmer Form Board, The Ohio Literacy Test, Morgan's Mental Test. The authors conclude that none of these equals the Stanford-Binet test as a single measure of general ability. The Myers' Mental Measure is the only other good test of general intelligence. The remaining tests have clinical rather than quantitative value.

In those cases in which the motor handicap was so severe as to make psychological tests quite inapplicable mental estimates were resorted to. The value of careful observation is shown in an interesting and enlightening manner. Here the method is to observe what situations are reacted to rather than the quality of the reactions, since the variety of reactions is so very limited. This method has been used formerly and has even entered into standardized tests (*e. g.*, Kuhlmann test at 18 months "Recognizing Objects in Pictures"), but, as the authors suggest, it has received relatively little attention.

Evidence is claimed for delayed mental growth—even after the age set for mental maturity—in birth-injured subjects. In view of the particular inadequacy of mental tests in measuring the ability of birth-injured subjects, however, this evidence does not appear to be very conclusive. The increments in mental age scores may be suspected of being attenuated learning curves.

The methods used in physical therapy are described. The evaluation of this form of treatment is shown to be a difficult matter. The effects of treatment and growth are inextricably intertwined. The apparent increase in mental alertness may be a direct effect of the treatment or due to the stimulating effect of an increased aura of attention. In addition, the period of observation was short.

In their study of the birth-injured the authors embarked on three lines of investigation—the clinical description of the condition, the adapting of methods of mental measurement, and the evaluating of physical therapy in these cases. No one of these has progressed sufficiently to completely clarify its relationship to the others, and thus give a real unity to the investigation. The diagnosis of birth injury is still uncertain. The interpretation of test results remains unsatisfactory. The observation of physical therapy has been short and lacks definite means of evaluation. The book serves its purpose in directing attention to this important problem and in outlining a method of investigation.

S. J. W. Horne.

PHYLOANALYSIS. A STUDY IN THE GROUP OR PHYLETIC METHOD OF BEHAVIOR ANALYSIS. By *William Galt, M.A.* (London: Kegan Paul, Trench, Trubner & Co., Ltd., 1933.)

With indifferent success the reviewer has endeavored to read this book, and has found it somewhat difficult to take it seriously; which is of course only another way of saying that all may not share the same pet hobbies or theories. Phyloanalysis, one gathers, is a sort of psychoanalysis applied openly to the group instead of privately to the individual. It also seems to have features in common with the third Oxford movement, one of whose principles, we are told, is "sharing." One conjectures that something akin to sharing is part of the technique of the cult of phyloanalysis. Possibly one might describe it as a benign blending of Freud and Buchman.

In the present pocket volume of 150 pages, one of the "Psyche Miniatures," the author, a disciple of Dr. Trigant Burrow, the originator of the system, attempts to set forth this technique. At this point we quote another reviewer, Professor Austin G. Schmidt, editor of the Loyola Educational Digest: "In a very frank preface Dr. Burrow declares that Dr. Galt has not succeeded in making the technique clear, which obviously excuses the reviewer from saying more."

C. B. F.

HYGIENE OF THE MIND. By *Baron Ernst von Feuchtersleben,* translated from the German by *F. C. Sumner, Ph.D.* (New York: The Macmillan Company, 1933.)

Professor Sumner has done English readers a service by making available in translation this significant treatise—*Zur Diätetik der Seele*—written by the Austrian physician von Feuchtersleben in 1838.

The principles of mental hygiene are not so new as its modern designation might suggest. From Greek philosophy onward, the great thinkers in the realm of human social relations and individual discipline have contributed their portion. The world-wide Mental Hygiene Movement to-day seeks to apply this accumulated wisdom of the centuries by organized and directed effort in specific fields of human welfare.

In Feuchtersleben one encounters reflections which might be termed naïve, one feels at home in discussions which smack of modernity, one is impressed throughout by that strong and wholesome *communis sensus* which is timeless.

His first words sound the keynote of his reasoning:

"Our age is fast, impetuous and frivolous. One does himself and the reading public a real mental service if one directs the gaze away from the discouraging life of a volcanic present, ... toward the quiet regions of the science of the inner man, toward the contemplation of our self."

Other quotations here and there will carry the theme forward. "If faith heals you, are you then less healed than if iron or quinine had healed you? . . . . Since art is trained ability, and if man has come to the point that life itself is an art for him, why should it not be possible that health, which is the life of life, become an art for him? This now is the hygiene of the

soul (the soul of hygiene—as one of our critics has in a friendly and striking manner put it) of which I speak. . . . . The mind of man is a single, integral, indivisible power and all that can be differentiated in it are the forms of its activity, in which it expresses itself. . . . . How deeply and dangerously do those unfortunate ones suffer who abandon themselves to the fixed idea of an ailment threatening them, or fancied as already present? Sooner or later they actually bring it about. . . . . If I become sick because I imagine myself to be sick, should I not be able to preserve myself healthy by imagining myself to be so? . . . . Consider your brother good and he is good; trust the half-good, and he *becomes* good. Expect abilities of your pupil, and he will develop them; regard him as unteachable, and he will remain so. Declare yourself healthy, and you may become so. The whole of nature is indeed but an echo of the mind, and the supreme law which may be discovered in her is: That from the ideal comes the real; that the idea gradually fashions the world after itself. . . . . Most people who have written of the emotions appear not to speak of natural things which are subject to the law of the universe, but of things which are outside of nature. . . . . Hate, anger, envy follow from the same necessity as everything else; they consequently recognize definite causes, by means of which they can be understood. . . . . There is hence no more effective and splendid means of taming the emotions than the understanding of them. . . . . We cannot, although we would like to, enjoy a free, pure existence, for a single, great, universal, unavoidable lie surrounds us—the lie involved in social intercourse. . . . . No one has the courage to be himself. . . . . To act a rôle throughout the whole of one's life, and to be able to say with the same right as Augustus in the concluding scene, *Plaudite!*—must wear one out prematurely."

Feuchtersleben counsels intellectual honesty; he cites numerous illustrations of the power of the mind over the body, and urges the cultivation of auto-suggestion; he reckons a devout and sustained friendship with nature as the sovereign restorer and preserver of mental health; finally he recommends as an extension of his own teaching, a perusal of the *Meditations of Marcus Aurelius.*

And so one spends a profitable hour, or evening, with a teacher of one hundred years ago.

C. B. F.

In Memoriam.

HENRY A. COTTON.

Among 1933's losses from the ranks of psychiatrists there is an outstanding and unexpected and premature one, that of Henry A. Cotton. Born in Norfolk in 1869, a graduate of the University of Maryland Medical School in 1899, he had his first contact with psychiatry at the historical Bay View Asylum, which some time in the eighties had given G. Stanley Hall the opportunity to connect the study of the normal and the abnormal and to broaden America's ways of studying human nature. Through Stewart Paton, Cotton was led to join the group of workers at the Worcester (Massachusetts) State Hospital in 1900. An active temperament, he took hold of his apprenticeship with wholesome interest and at the same time with an ever active social interest in the surrounding world. From time to time he would come to me to discuss his visions of opportunities, in the work at hand and in such matters as the consideration of the superintendency of the Worcester City Hospital suggested to him by men who recognized his talents. On each occasion he would become only more determined to make a mark in psychiatry, encouraged in his steadfastness by the one who later became his wife. He undertook the bedside and post-mortem study of tabes in paresis, a creditable piece of personal work and correlation. Shortly after he had been attracted to a post at the Danvers Hospital which enabled him to marry, he decided to take a period of study in Kraepelin's new Clinic and with Alzheimer (1905-1907) and as a result he brought out some studies of value—on central neuritis and fatty changes in the cortex of melancholia cases. Not long after his return to this country, in 1907, the position as medical director of the state hospital at Trenton, N. J., was offered him. The hospital at which Dorothy Dix spent the last years of her pioneer life, underwent at once a most noteworthy transformation through the radical abolition of restraint and the start of a steady string of investigations such as heredity studies, and soon after that the radical treatment of pare-

sis with endolumbar and endoventricular treatment. From this there was but a short step to what made Cotton the protagonist of the focal infection theory and what is more, that of the practical working out of the surgical treatment of his patients. In this he was first helped by the surgeon, J. W. Draper, and an enthusiastic clinical laboratory worker, T. W. Hastings. It was in keeping with Cotton's temperament that he developed his own surgical technique and a surgical service which gave his hospital practice a unique stamp. After the death of Dr. Draper, Dr. Cotton practically took over the entire responsibility and actual work. Of late years, there were from time to time threats of ill health from cardiorenal disturbance. In 1930 he retired from the active directorship of the hospital to the position of director of research and to his private practice. On May 8, 1933, death overtook him in the midst of a full day's activity. A few years before his death he had acquired a home near Princeton in which he took great satisfaction and from which he carried on his work in connection with the Mercer Hospital at Trenton.

Dr. Cotton laid down his conceptions and gave an account of the results of his work in lectures that he gave at Princeton in January, 1921, on "The Defective, Delinquent, and Insane," and in numerous communications. A man of action and of results, he made an extraordinary record of achievement. His views and practice were a vigorous challenge which stood non-compromisingly for an almost unitary explanation by focal infections, supported by the testimony of numerous patients and a number of colleagues, and contested by an equally non-compromising attitude of non-surgically inclined colleagues in the rising wave of variously inclusive psychogenic interpretations. The hope that Dr. Cotton himself might obtain the support of one or another of the foundations promoting research was only partially fulfilled and the analysis of the tremendous amount of work was but slowly progressing at the time of his death and now will have to be carried on without the leading and active spirit of the sincere and convinced protagonist. A devoted husband and a devoted father of his two sons, Dr. Cotton leaves a heritage also to the psychiatric family and the many friends. It entails the obligation of a full evaluation of his life-work which can only be given in the light of prolonged observation and comparison. The history of the developments at the

Trenton State Hospital is a most remarkable achievement of the pioneer spirit, and the history of Dr. Cotton one of a remarkable example of energy, purpose and wholeheartedness. As a physician and as a friend and colleague, he will always be remembered as one of the most stimulating figures of our generation.

ADOLF MEYER.

SHEPHERD IVORY FRANZ.

Dr. Franz died on October 14, 1933, at the age of 59. A student of physiology and psychology, his first post after receiving the doctorate of psychology from Columbia University was as assistant in physiology at the Harvard Medical School. In addition to other appointments he also served as psychologist and director of research at St. Elizabeth's, the government hospital for the insane in Washington, D. C. During the last nine years of his life he was connected with the University of California at Los Angeles as head of the department of psychology. These were years of distinguished service to the institution and to the community.

He was author of numerous scientific publications. Among the most outstanding of these were "A Handbook of Mental Examination Methods," 1912, second edition 1919; "Nervous and Mental Re-Education," 1923, for which he was awarded the Butler Medal; "How the Brain Works," this being a faculty research lecture at the University of California at Los Angeles delivered in 1926; "Persons One and Three," 1933, being an account of the case of an aphasic person.

His work on the localization of function in the brain of men and animals has far-reaching significance. His work as teacher, editor, and scientist has placed his generation under a lasting debt.

KATE GORDON.